

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS	)	
CORPORATION,	)	
	)	
Plaintiff	)	
	)	C.A. No. 23-975 (RGA) (SRF)
v.	)	
	)	REDACTED - PUBLIC VERSION
LIQUIDIA TECHNOLOGIES, INC.,	)	
	)	
Defendant.	)	

**VOLUME 1 OF 2 OF**  
**PROPOSED JOINT PRETRIAL ORDER**

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FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff

v.

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Defendant.

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C.A. No. 23-975 (RGA) (SRF)

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May 23, 2025

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## **I. INTRODUCTION**

1. Plaintiff United Therapeutics Corporation (“Plaintiff” or “UTC”) and Defendant Liquidia Technologies, Inc. (“Defendant” or “Liquidia”) submit this Proposed Final Pretrial Order pursuant to the Court’s Scheduling Order (*see* D.I. 45) and D. Del. LR 16.3(c) in advance of the Pretrial Conference scheduled to be held in person on Friday, May 30, 2025, at 2:00 pm ET.

2. A three-day bench trial is scheduled to begin on June 23, 2025.

## **II. NATURE OF THE CASE AND PLEADINGS**

3. This is a Hatch-Waxman action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, §§ 100, *et seq.*, and an action for declaratory judgment pursuant to the Declaratory Judgment Act, 28 U.S.C. §§ 2201, *et seq.*, involving U.S. Patent No. 11,826,327 (the “’327 patent” or “Patent-in-Suit”). This action arises out of Liquidia’s submission of New Drug Application No. 213005 and an amendment thereto, filed under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and pursuant to 21 U.S.C. § 355(b)(2) (the “505(b)(2) Application”), to the U.S. Food and Drug Administration (“FDA”) seeking approval to engage in the commercial manufacture, use, or sale of YUTREPIA™ (treprostinil) for the treatment of pulmonary hypertension associated with interstitial lung disease (“PH-ILD”) to improve exercise ability (“Defendant’s Proposed Product”) before the expiration of the Patent-in-Suit.

### **A. United Therapeutics Corporation**

4. UTC is a corporation organized and existing under the laws of the State of Delaware and having a place of business at 1000 Spring Street, Silver Spring, Maryland 20910. UTC is an innovative biotechnology company focused on the development and commercialization of products designed to address the needs of patients with chronic and life-threatening conditions.



UTC researches and develops treatments for cardiovascular and pulmonary diseases, pediatric cancers, and other orphan diseases.

5. UTC makes, markets, and sells in the United States TYVASO<sup>®</sup> (treprostinil) inhalation solution, which was first approved by the FDA in 2009, and TYVASO DPI<sup>®</sup> (treprostinil) inhalation powder, which was approved by the FDA in 2022. Both TYVASO<sup>®</sup> and TYVASO DPI<sup>®</sup> are approved for the treatment of PH-ILD to improve exercise capacity. TYVASO DPI<sup>®</sup> (treprostinil) inhalation powder is the first marketed dry powder formulation of treprostinil in the United States.

6. UTC owns the '327 patent and listed it, along with other patents, in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book").

**B. Liquidia Technologies, Inc.**

7. Liquidia is a corporation organized and existing under the laws of the State of Delaware, with a registered office at 251 Little Falls Drive, Wilmington, Delaware 19808, and a principal place of business at 419 Davis Drive, Suite 100, Morrisville, North Carolina 27560. Liquidia is a biopharmaceutical company focused on the development and commercialization of innovative therapeutics using its proprietary PRINT<sup>®</sup> technology to transform the lives of patients.

8. Liquidia's Product, YUTREPIA<sup>™</sup>, is a dry powder formulation of treprostinil, was designed using Liquidia's proprietary PRINT<sup>®</sup> technology to enhance deep-lung delivery using a convenient, palm-sized, low-resistance, disposable dry powder inhaler ("DPI") for the treatment of pulmonary arterial hypertension. Liquidia's proprietary PRINT<sup>®</sup> technology allows for particles of a precise size and highly uniform shape.

9. YUTREPIA<sup>™</sup> has the potential to maximize the therapeutic benefits of treprostinil in treating PAH by safely delivering higher doses into the lungs compared to currently approved

conventional inhaled therapies, including TYVASO® and TYVASO DPI®. YUTREPIA™ is also more convenient to use than currently approved nebulized therapies, including TYVASO®, as YUTREPIA™ is more conveniently administered and contained in a small carrying pouch as opposed to a nebulizer.

**C. Pleadings and Orders**

10. Plaintiff sued Defendant for infringement of U.S. Patent No. 10,716,793 on September 5, 2023, based on Defendant's submission of the 505(b)(2) Application to FDA. *See* D.I. 1.

11. On November 30, 2023, Plaintiff filed the First Amended Complaint alleging infringement of the '327 patent in addition to the '793 patent, based on Defendant's submission of the 505(b)(2) Application to FDA. *See* D.I. 8.

12. On January 8, 2024, Defendant filed an answer to the First Amended Complaint, affirmative defenses for failure to state a claim, non-infringement, invalidity, prosecution history estoppel, inequitable conduct, and collateral estoppel, and counterclaims seeking declaratory judgments that the '327 patent is invalid, not infringed, and unenforceable. *See* D.I. 12.

13. On January 22, 2024, the parties' stipulation to dismiss, without prejudice, Counts I and II of Plaintiff's First Amended Complaint regarding Plaintiff's allegations of infringement of the '793 patent was So Ordered by the Court. *See* D.I. 17.

14. On February 26, 2024, Plaintiff filed a motion for a preliminary injunction. *See* D.I. 25.<sup>1</sup>

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<sup>1</sup> Plaintiff's opening brief was filed concurrently on February 26, 2024 (*see* D.I. 26), Defendant's answering brief in opposition to Plaintiff's motion for a preliminary injunction was filed on April 1, 2024 (*see* D.I. 52), and Plaintiff's reply brief in support of its motion for preliminary injunction was filed on April 15, 2024 (*see* D.I. 65).

15. On February 28, 2024, Plaintiff filed an answer to Defendant’s counterclaims. *See* D.I. 32.

16. On May 31, 2024, the Court issued a Memorandum Order denying Plaintiff’s motion for a preliminary injunction. *See* D.I. 96.

17. The Court issued a Claim Construction Order on October 21, 2024, construing the preamble of the ’327 patent as limiting, as agreed by the parties, and three disputed terms of the ’327 patent—“a”/“the,” “maximum tolerated dose,” and “pulsed inhalation device.” *See* D.I. 155. The Court also held that “maximum tolerated dose” was not indefinite.

### **III. JURISDICTION AND STANDING**

18. This action arises under the patent laws of the United States, 35 U.S.C. §§ 100 *et seq.* This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

19. For purposes of this action, no party contests personal jurisdiction in this Court.

20. For purposes of this action, no party contests venue in this Court.

21. For purposes of this action, Plaintiff has standing as the lawful owner of the Patent-in-Suit by assignment of all right, title and interest in and to the Patent-in-Suit, including the right to bring infringement suits thereon, and Defendant does not dispute Plaintiff’s standing. Defendant agrees that Plaintiff need not present proof of this at trial.

### **IV. UNCONTESTED FACTS**

22. The parties stipulate to and admit the facts listed in Exhibit 1. These uncontested facts require no proof at trial and will become part of the evidentiary record in this case.

### **V. CONTESTED FACTS**

23. Plaintiff’s statement of issues of fact that remain to be litigated is attached as

Exhibit 2.

24. Defendant's statement of issues of fact that remain to be litigated is attached as

Exhibit 3.

25. If any statement in a party's statement of issues of fact that remain to be litigated should properly be considered an issue of law, then such statement shall be so considered as an issue of law.

## **VI. ISSUES OF LAW**

26. Plaintiff's statement of issues of law that remain to be litigated is attached as Exhibit 4.

27. Defendant's statement of issues of law that remain to be litigated is attached as Exhibit 5.

28. If any statement in a party's statement of issues of law that remain to be litigated should properly be considered an issue of fact, then such statement shall be so considered as an issue of fact.

## **VII. EXHIBITS**

29. The list of pre-marked trial exhibits that may be offered by Plaintiff, including Defendant's objections thereto, is attached as Exhibit 10. Plaintiff's trial exhibits will be identified with PTX numbers, and Plaintiff's demonstratives will be identified with PDX numbers.

30. The list of pre-marked trial exhibits that may be offered by Defendant, including Plaintiff's objections thereto, is attached as Exhibit 11. Defendant's trial exhibits will be identified with DTX numbers, and Defendant's demonstrative exhibits will be identified with DDX numbers.

31. The joint list of pre-marked trial exhibits that may be offered by any party is attached as Exhibit 12. The parties' joint trial exhibits will be identified by JTX numbers.

32. The parties shall meet and confer in good faith to agree to a single set of any translated documents for trial.

33. Plaintiff and Defendant each reserve the right to offer exhibits set forth on the other's exhibit list, even if not set forth on its own exhibit list, except that the offering party reserves the right to raise objections to the use of the exhibit by the opposing party. All objections to such exhibits are preserved. For clarity, Plaintiff and Defendant each reserve the right to raise objections to the use of any exhibit, even if set forth on its own exhibit list. The parties shall not remove a document once it has been added to the party's exhibit list without agreement from the other party, unless it provides the other party the opportunity to add the document to its exhibit list. Further, Plaintiff and Defendant each reserve the right to raise objections to the use of an exhibit from the Joint Exhibit List by the opposing party.

34. Supplementation of exhibits lists will be permitted until after the pre-trial conference and this order has been accepted and signed by the Court after which further supplementation of exhibits shall only be permitted with good cause shown or by agreement of the parties. Notwithstanding the language in this paragraph, supplementation of exhibit lists will be permitted for documents produced within families of documents listed on either parties' exhibit list or the joint trial exhibit list, to the extent supplementation is necessary to authenticate a trial exhibit or to lay foundation for a witness' knowledge of a trial exhibit.

35. Exhibits to which no objection has been made that are offered into evidence at trial are received in evidence by operation of this Order, without any need for further foundation testimony, provided they are used with a witness whether appearing live or by deposition. Any exhibit, once admitted, may be used equally by each party, except that nothing herein shall be construed as a stipulation or admission that the document is entitled to any weight in deciding the

merits of this case. Statements by a party opponent from any interrogatory responses, or other discovery responses, or pleadings may also be read into the record at trial.

36. Except for exhibits to be used solely for purposes of impeachment, Exhibits 10, 11, and 12 comprise the exhibits that may be introduced at trial. All documents, whether offered on direct or cross-examination, must be included on a trial exhibit list to be admitted into evidence and any such document not listed in any of Exhibits 10, 11, and 12 will not be entered into evidence at trial, absent good cause shown.

37. The parties stipulate to the authenticity of the documents listed in the attached exhibit lists unless such objections are specifically and expressly preserved therein. The parties further agree that they will not dispute the authenticity of any document that was produced during discovery, which on its face appears to have been authored by an employee, officer or agent of the producing party in the ordinary course of business, and that such documents shall be deemed *prima facie* authentic, subject to the right of the party against whom such a document is offered to adduce evidence to the contrary or to require the offering party to provide authenticating evidence if the opposing party has a reasonable basis to believe that the document is not authentic. For the avoidance of doubt, Plaintiff will not object to documents produced by UTC on the basis of authenticity and Defendant will not object to documents produced by Liquidia on the basis of authenticity.

38. The parties reserve the right to object to the introduction into evidence of the documents and files referenced in the preceding paragraph (in whole or in part) on all other grounds, including the admissibility of these documents for reasons other than challenging their authenticity or status as inadmissible hearsay. Each party reserves the right to object under FRE 105, 106, 401, 402, and 403 to any exhibit offered by another party, at the time such exhibit is

offered, in view of the specific context in which such exhibit is offered.

39. The listing of a trial exhibit does not constitute an admission as to the admissibility of the trial exhibit (i.e., a waiver of any applicable objection).

40. The parties agree that any description or date for a document reflected on an exhibit list is provided for convenience only and shall not be used as an admission or otherwise as evidence regarding the content or date of the listed document or any other listed documents.

41. Legible copies of documents may be offered and received into evidence to the same extent as an original.

**A. Demonstrative Exhibits**

42. The parties may use demonstrative exhibits, which do not need to be identified on their respective lists of trial exhibits.

43. Each demonstrative exhibit shall identify by exhibit number and/or Bates number all trial exhibits that form the basis of the demonstrative exhibit.

44. Demonstratives shall be submitted to the Court at the end of trial and included in the record for appeal.

45. Each party will exchange PDF files or PPTX files of full color copies of demonstrative trial exhibits by e-mail by 6:30 p.m. ET one calendar day before they will be used at trial. However, demonstrative exhibits to be used with opening statements should be exchanged via e-mail by 5:00 p.m. ET one calendar day before the day opening statements are to be given. For video or animations, the party seeking to use the demonstrative will provide it to the other side in an appropriate electronic format to view the video or animation. For irregularly sized physical exhibits, the party seeking to use the demonstrative will provide a color representation as a PDF of 8.5 x 11 copies of the exhibits. For example, demonstrative trial exhibits intended for use at trial

on Monday, June 23, 2025, would be exchanged by e-mail before 6:30 p.m. ET on Sunday, June 22, 2025, except the demonstrative exhibits intended for use with opening statements would be exchanged by e-mail before 5:00 p.m. ET on Sunday, June 22, 2025. The parties do not need to exchange in advance any demonstrative exhibits that are used solely on cross-examination of a witness.

46. The party receiving identification of demonstrative trial exhibits shall inform the party identifying the demonstrative trial exhibits of any objections by 8:30 p.m. ET on the day of receipt, and the parties shall meet and confer as soon as possible thereafter but by no later than 9:30 p.m. ET to resolve such objections. However, with respect to identification of demonstrative trial exhibits to be used with opening statements, the party receiving identification of such demonstrative trial exhibits shall inform the party identifying the exhibits of any objections by 8:30 p.m. ET on the day of receipt, and the parties shall meet and confer as soon as possible thereafter but by no later than 9:30 p.m. ET to resolve such objections. Any unresolved objections shall be brought to the Court's attention for resolution no later than the start of the trial day on which the demonstrative exhibit is intended to be used. The provisions in this and the two preceding paragraphs do not apply to demonstratives created during testimony or argument at trial or to demonstratives to be used for cross examination, neither of which need to be provided to the other side in advance of their use. In addition, highlighting, ballooning, arrowing, call-outs, excerpting, etc., of exhibits or parts of exhibits or testimony are not required to be provided to the other side in advance of their use.

**B. Trial Exhibits**

47. Each party will also provide by e-mail to opposing counsel a list of all exhibits (by exhibit number) a party intends to use in direct examination of non-adverse witnesses by 6:30 p.m.



# EXHIBIT 1

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff,

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

C.A. No. 23-00975-RGA-SRF



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**EXHIBIT 1: JOINT STATEMENT OF UNCONTESTED FACTS**

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## **I. INTRODUCTION**

1. In accordance with Local Rule 16.3(c)(3) of the Local Rules of Civil Practice and Procedure of the United States District Court for the District of Delaware, Plaintiff United Therapeutics Corporation (“Plaintiff” or “UTC”) and Defendant Liquidia Technologies, Inc. (“Defendant” or “Liquidia”) submit the following joint statement of the facts that are admitted and require no proof with respect to the Patent-in-Suit identified in Section II.A.

## **II. THE PARTIES AND NATURE OF THE CASE**

2. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, Sections 100 *et seq.*, involving United States Patent No. 11,826,327 (“the ’327 patent”). This action arises out of Defendant’s submission of New Drug Application (NDA) No. 213005 and a July 24, 2023 amendment thereto (“Defendant’s NDA”), filed under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act and pursuant to 21 U.S.C. § 355(b)(2), submitted to the U.S. Food and Drug Administration (FDA) and seeking approval to engage in the commercial manufacture, use, or sale of Yutrepia™ for the indication of pulmonary hypertension associated with interstitial lung disease (“PH-ILD”).

3. Plaintiff is a corporation organized and existing under the laws of the State of Delaware and having a place of business at 1040 Spring Street, Silver Spring, Maryland 20910.

4. Plaintiff holds NDA No. 022387, which has been approved for Tyvaso® (treprostinil) Inhalation Solution, 0.6 mg/ml.

5. Plaintiff holds NDA No. 214324, which has been approved for Tyvaso DPI® (treprostinil) Inhalation Powder.

6. Defendant is a corporation organized and existing under the laws of the State of Delaware, with a registered office at 251 Little Falls Drive, Wilmington, Delaware 19808, and a

principal place of business at 419 Davis Drive, Suite 100, Morrisville, North Carolina 27560.

7. Defendant's NDA and amendment were submitted to the FDA before issuance of the '327 patent.

8. Defendant's NDA contains a "Paragraph IV" certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) directed to the '327 patent. Defendant sent Plaintiff a "Notice Letter" dated December 12, 2023, which informed Plaintiff that Defendant's NDA contained, *inter alia*, a Paragraph IV certification regarding the '327 patent.

9. Plaintiff commenced this action before the expiration of forty-five days from the date it received Defendants' initial Notice Letter, dated July 24, 2023.

10. The Court has personal jurisdiction over the parties, subject matter jurisdiction for this matter, and venue is proper in this Court.

### **III. THE PATENT-IN-SUIT**

#### **A. The '327 Patent**

11. Plaintiff asserts claims 1-11 and 14-19 of the '327 patent.

12. The '327 patent is titled "Treatment For Interstitial Lung Disease."

13. The '327 patent issued on November 28, 2023 from U.S. Patent Application No. 17/233,061 ("the '061 application), filed on January 31, 2020.

14. The '327 patent lists on its face the named inventors Leigh Peterson, Peter Smith, and Chunqin Deng.

15. The '327 patent and the '061 application claim priority to U.S. Provisional Patent Application No. 63/011,810, filed on April 17, 2020 and Provisional Application No. 63/160,611, filed on March 12, 2021.

16. The Orange Book lists the expiration of the '327 patent as February 3, 2042.

**B. Claim Construction**

17. On October 21, 2024, the Court construed the terms below to have the following meanings (D.I. 155):

Claim Term	Claim Construction
“A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease” '327 patent, claim 1	This preamble is limiting, as agreed by the parties
“a” / “the” in the following terms: “a patient,” “the patient,” “a maximum tolerated dose,” “a single administration event,” “the administering,” and “the single inhalation administration event” '327 patent, claims 1-5, 8-10, and 15-19	“one or more”
“maximum tolerated dose” '327 patent, claim 1	plain and ordinary meaning, not indefinite
“pulsed inhalation device” '327 patent, claims 11 and 14	“a device that provides for non-continuous inhaled drug delivery”

**IV. THE PARTIES' PRODUCTS**

**A. Plaintiff's Tyvaso® Product**

18. Plaintiff markets and sells Tyvaso® (treprostinil) Inhalation Solution, 0.6 mg/ml, under the registered U.S. Trademark Tyvaso®.

19. Tyvaso® was initially approved by the FDA in the United States in July 2009. Tyvaso® was approved in 2009 as indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. In 2021, Tyvaso® was approved as indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.

20. Tyvaso® is an inhalable product approved for sale in a 0.6 mg/ml concentration. Tyvaso® solution is placed into a nebulizer, aerosolized by the nebulizer, and inhaled by the patient.

21. The Patent-in-Suit is listed in connection with Tyvaso<sup>®</sup> in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations publication (the "Orange Book").

**B. Plaintiff's Tyvaso DPI<sup>®</sup> Product**

22. Plaintiff markets and sells Tyvaso DPI<sup>®</sup> (treprostinil) Inhalation Powder, under the registered U.S. Trademark Tyvaso DPI<sup>®</sup>.

23. Tyvaso DPI<sup>®</sup> was approved by the FDA in the United States on May 23, 2022 as indicated for the treatment of both PAH (WHO Group 1) and PH-ILD (WHO Group 3) to improve exercise ability.

24. Tyvaso DPI<sup>®</sup> is an inhalable product approved for sale in single-dose plastic cartridges in 5 strengths: 16 mcg, 32 mcg, 48 mcg, 64 mcg, and 80 mcg. Tyvaso DPI<sup>®</sup> cartridges are loaded into a Tyvaso DPI<sup>®</sup> Inhaler and inhaled by the patient.

25. The Patent-in-Suit is listed in connection with Tyvaso DPI<sup>®</sup> in the FDA's Orange Book.

**C. Defendant's Proposed Yutrepia<sup>™</sup> Product**

26. Defendant's Proposed Product will be sold under the tradename Yutrepia<sup>™</sup>.

27. Defendant's internal development name for Defendant's Proposed Product was "LIQ861."

28. Yutrepia<sup>™</sup> is a dry powder formulation of treprostinil sodium contained in capsules in 4 strengths: 26.5 mcg, 53 mcg, 79.5 mcg, and 106 mcg.

29. Yutrepia<sup>™</sup>'s dry powder formulation will be delivered to patients via inhalation using a supplied capsule-based inhaler.

30. Defendant's NDA was originally submitted to FDA on January 24, 2020.

31. On November 5, 2021, Yutrepia<sup>™</sup> received tentative FDA approval for the

treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability in patients with NYHA Functional Class II-III symptoms.

32. On July 24, 2023, Defendant filed an amendment to its NDA that added the indication “[t]reatment of patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability” to the Proposed Product’s label.

33. On August 16, 2024, the FDA granted Defendant tentative approval to market and sell the Proposed Product in the United States, including for its PH-ILD indication.

34. Defendant’s Proposed Product will be supplied with a package insert (“Proposed Label”), which provides information regarding that Product and how it should be administered.

35. Defendant’s Proposed Label describes Defendant’s Proposed Product as being “indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.”

36. Defendant is currently performing a clinical trial of Defendant’s Proposed Product in PH-ILD patients entitled “An Open-Label Prospective Multicenter Study to Evaluate Safety and Tolerability of Dry Powder Inhaled Treprostinil in Pulmonary Hypertension” (the “ASCENT study”).



# EXHIBIT 2

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff,

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

C.A. No. 23-00975-RGA-SRF



**EXHIBIT 2: PLAINTIFF'S STATEMENT OF CONTESTED FACTS**

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## **I. INTRODUCTION**

In accordance with Local Rule 16.3(c)(3) of the Local Rules of Civil Practice and Procedure of the United States District Court for the District of Delaware, Plaintiff United Therapeutics Corporation (“Plaintiff” or “UTC”) submits the following statement of contested facts with respect to United States Patent No. 11,826,327 (the “’327 patent”) (the “Patent-in-Suit”).

The following statements are meant to serve as an overview of the contested facts to be litigated at trial. Accordingly, Plaintiff reserves the right to provide any background facts to support the contested facts set forth herein, and to prove additional details regarding the below facts that have been identified throughout the discovery process including facts identified in expert reports. Plaintiff further intends to offer evidence to rebut evidence offered by Liquidia Technologies, Inc. (“Defendant” or “Liquidia”). Plaintiff reserves the right to modify or amend this Exhibit to the extent necessary to reflect any future rulings by the Court, and to supplement or amend this Exhibit to fairly respond to any new issues that Defendant may raise. To the extent Plaintiff’s statement of the issues of law that remain to be litigated, which is submitted as Exhibit 4 hereto, contains issues of fact, those issues are incorporated herein by reference. Moreover, if any issue of fact identified below should properly be considered an issue of law, then such statement should be considered to be part of Plaintiff’s statement of issues of law that remain to be litigated. Plaintiff incorporates by reference its expert reports and declarations in support of any proof to be presented by expert testimony.

### **A. Nature and Stage of the Proceedings**

1. This is a Hatch-Waxman action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, §§ 100, *et seq.*, and an action for declaratory judgment pursuant to the Declaratory Judgment Act, 28 U.S.C. §§ 2201, *et seq.*, involving the ’327 patent. This action arises out of Liquidia’s submission of New Drug Application

No. 213005 and an amendment thereto, filed under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and pursuant to 21 U.S.C. § 355(b)(2) (the “505(b)(2) Application”), to the U.S. Food and Drug Administration (“FDA”) seeking approval to engage in the commercial manufacture, use, or sale of YUTREPIA™ (treprostinil) for the treatment of pulmonary hypertension associated with interstitial lung disease (“PH-ILD”) to improve exercise ability (“Defendant’s Proposed Product”) before the expiration of the Patent-in-Suit.

**B. Background of the Parties**

2. UTC is a corporation organized and existing under the laws of the State of Delaware and having a place of business at 1000 Spring Street, Silver Spring, Maryland 20910. UTC is an innovative biotechnology company focused on the development and commercialization of products designed to address the needs of patients with chronic and life-threatening conditions. UTC researches and develops treatments for cardiovascular and pulmonary diseases, pediatric cancers, and other orphan diseases.

3. Plaintiff holds NDA No. 022387, which has been approved for Tyvaso® (treprostinil) Inhalation Solution, 0.6 mg/ml.

4. Plaintiff holds NDA No. 214324, which has been approved for Tyvaso DPI® (treprostinil) Inhalation Powder.

5. UTC makes, markets, and sells in the United States TYVASO® (treprostinil) inhalation solution, which was first approved by the FDA in 2009, and TYVASO DPI® (treprostinil) inhalation powder, which was approved by the FDA in 2022.

6. Both TYVASO® and TYVASO DPI® are approved for the treatment of PH-ILD to improve exercise capacity. TYVASO DPI® (treprostinil) inhalation powder is the first marketed dry powder formulation of treprostinil in the United States.

7. UTC owns the ’327 patent and listed it, along with other patents, in FDA’s



Approved Drug Products with Therapeutic Equivalence Evaluations (“Orange Book”).

8. Liquidia is a corporation organized and existing under the laws of the State of Delaware, with a registered office at 251 Little Falls Drive, Wilmington, Delaware 19808, and a principal place of business at 419 Davis Drive, Suite 100, Morrisville, North Carolina 27560.

9. Defendant’s § 505(b)(2) Application was submitted to the FDA prior to the expiration date of the ’327 patent.

10. Defendant’s § 505(b)(2) Application contains a “Paragraph IV” certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) directed to the ’327 patent. Defendant sent Plaintiff a “Notice Letter” dated December 12, 2023, which informed Plaintiff that Defendant’s § 505(b)(2) Application contained, *inter alia*, a Paragraph IV certification regarding the ’327 patent.

11. Plaintiff commenced this action before the expiration of forty-five days from the date it received Defendants’ initial Notice Letter, dated July 24, 2023.

12. The Court has personal jurisdiction over the parties, subject matter jurisdiction for this matter, and venue is proper in this Court.

**C. Plaintiff UTC’s Experts**

13. Dr. Steven Nathan is a board-certified physician in pulmonary diseases and internal medicine, licensed to practice in Virginia. He earned his M.B.B.cH degree from the University of Witwatersrand in South Africa (equivalent to an M.D.) and completed his residency and fellowships in pulmonary, critical care, and lung transplantation medicine in the United States. Since 1996, Dr. Nathan has served in senior clinical roles at Inova Fairfax Medical Center, including Director of the Advanced Lung Disease and Lung Transplant Programs. He also holds academic appointments and currently serves as a professor of medical education at the University of Virginia. Dr. Nathan has authored over 550 scientific publications, more than 200 of which concern interstitial lung disease. He has extensive clinical and research experience in pulmonary

hypertension (PH), including PH associated with interstitial lung disease (PH-ILD), and has led or participated in numerous clinical trials and guideline initiatives. His qualifications place him well above the level of a person of ordinary skill in the art (POSA), and he offers expert testimony in this matter regarding infringement of the '327 patent from that perspective.

14. Dr. Ronald Thisted is a biostatistics expert with over five decades of experience in the fields of biostatistics, epidemiology, clinical trial design, and the statistical analysis of medical interventions. He holds a Ph.D. in statistics from Stanford University and is Professor Emeritus at the University of Chicago, where he held appointments in the Departments of Statistics, Public Health Sciences, Anesthesia & Critical Care, and the Committee on Clinical Pharmacology and Pharmacogenomics. During his tenure at the University, Dr. Thisted served in numerous leadership roles, including Chair of the Department of Health Studies and Vice Provost for Academic Affairs. He has authored over 100 peer-reviewed publications, taught extensively in biostatistics and clinical research methods—including courses required of all first-year medical students—and received the Quantrell Award for Excellence in Undergraduate Teaching. Dr. Thisted has consulted for the pharmaceutical and medical device industries since the 1970s, advising on the design and statistical analysis of Phase I–III clinical trials. He is a Fellow of both the American Statistical Association and the American Association for the Advancement of Science. His experience working closely with physicians in designing and analyzing clinical studies informs how a POSA would interpret clinical data as relevant to the '327 patent.

15. Dr. Bradley Wertheim is an associate pulmonary and critical care physician at Brigham and Women's Hospital in Boston and Co-Director of the Pulmonary Vascular Disease Section at the VA Boston Healthcare System. He serves as Director of the Rheumatic Pulmonary Vascular Disease Clinic, where he specializes in the early diagnosis and treatment of pulmonary

hypertension, including PH-ILD and other heart-lung interaction disorders. Board certified in Internal Medicine, Pulmonary Disease, and Critical Care Medicine, Dr. Wertheim has practiced as an attending physician since 2017 and has treated hundreds of patients with both pulmonary vascular disease and interstitial lung disease. He is also an Assistant Professor of Medicine at Harvard Medical School and has taught extensively on pulmonary vascular diseases at post-doctoral, continuing education, and international forums. He received his M.D. from Harvard, trained at Massachusetts General Hospital and Brigham and Women's Hospital, and completed advanced fellowships in pulmonary hypertension and pulmonary vascular biology. A published researcher with over 40 scientific works, Dr. Wertheim leads an NIH-funded laboratory focused on pulmonary vascular biology and fibrosis. He is qualified by education and experience to offer expert testimony, including on matters relevant to the skill level of a POSA.

16. Dr. Frederick Selck is a Managing Director at Secretariat Advisors, LLC, with extensive experience in health economics, econometrics, and biostatistics. He holds a Ph.D. in Applied Economics from Johns Hopkins University and a BA/MA in Economics from Hunter College – CUNY. Dr. Selck has held academic and government roles, including serving as a Senior Service Fellow at the CDC's National Center for Health Statistics and as a faculty member at Georgetown and Johns Hopkins Universities, where he teaches courses in microeconomics and health finance. He has published in and reviewed for leading peer-reviewed journals in health and medical research. Dr. Selck has been retained as an expert in numerous healthcare and life sciences matters, including those involving pharmaceutical markets, reimbursement systems, and alleged anticompetitive conduct. He has testified about competition between non-therapeutically equivalent drug products and has previously been certified as an expert in healthcare markets and health economics in court.

## **II. THE PATENT IN SUIT**

### **A. Overview**

17. Plaintiff asserts claims 1-11 and 14-19 of the '327 patent (the "Asserted Claims").

18. The '327 patent is entitled "Treatment for Interstitial Lung Disease," relates to the treatment of PH-ILD using inhaled treprostinil.

19. The '327 patent claims methods of improving exercise capacity in a patient suffering from PH-ILD by administering an effective amount of inhaled treprostinil.

20. The named inventors of the '327 patent are Leigh Peterson, Peter Smith, and Chunqin Deng. The named inventors are the correct inventors.

21. The '327 patent is assigned to UTC.

22. Plaintiff is the lawful owner of the '327 patent by assignment of all right, title, and interest in and to the '327 patent, including the right to bring infringement suits.

23. The '327 patent issued on November 28, 2023 from U.S. Patent Application No. 17/233,061 ("the '061 application"), filed on January 31, 2020.

24. The '327 patent and the '061 application properly claim priority to U.S. Provisional Patent Application No. 63/011,810, filed on April 17, 2020 ("the '810 Provisional"), and U.S. Provisional Patent Application No. 63/160,611, filed on March 12, 2021 ("the '611 Provisional").

25. The Orange Book lists the expiration date of the '327 patent as February 3, 2042.

### **B. The Asserted Claims**

26. The '327 patent has 19 claims, including independent claim 1 and a further 18 dependent claims.

27. Plaintiff asserts that Defendant infringes claims 1-11 and 14-19 of the '327 patent, reproduced below:

1. A method of improving exercise capacity in a patient having

pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.

**2.** The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.

**3.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.

**4.** The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.

**5.** The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

**6.** The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.

**7.** The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.

**8.** The method of claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.

**9.** The method of claim 1, wherein said administering provides a statistically significant improvement of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.

**10.** The method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8

weeks, 12 weeks, or 16 weeks of the administering.

**11.** The method of claim 1, wherein said administering is performed by a pulsed inhalation device.

**14.** The method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.

**15.** The method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg.

**16.** The method of claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient.

**17.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.

**18.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.

**19.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

28. Claim 1 describes a method “for improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease.” Each dependent claim (claims 2–7, 9–10, and 17–19) claims a method that increases, or provides an increase of, or provides a reduction, improves, or provides an improvement in a particular clinical outcome. Improvements are only attributed to practicing the claimed method when they exceed any improvements that result from not practicing the method described in the claims.

29. The preamble of claim 1 provides the purpose for which the claim must be performed.

30. The claims do not include patients with severe PH out of proportion with their lung

disease as they are categorized as Group 1 PAH patients.

31. The claims require that the claimed method's "administering" step "provide[]" or "increase[]" a parameter. The claims thus require that the administering is the cause of the "increase[]." Data comparing the effects of treprostinil treatment to that of the patient's baseline will not demonstrate that the administering step is the cause of the "increase[]" as other factors can contribute to favorable changes in the claimed parameters. Uncontrolled studies (e.g., those without a comparison of the treatment to placebo) cannot demonstrate the claimed treatment effects.

### **C. Specification**

32. The '327 patent specification describes the target patient population, the dire or progressive state of the disease, and the unsatisfactory first-line PH-ILD treatments. The '327 patent specification also describes the dosages of inhaled treprostinil and the modes of administration of treprostinil.

33. The specification of the '327 patent contains data from the INCREASE trial. Example 1 and 3 of the specification contain a discussion of INCREASE, including its design, patient population, protocol, endpoints, statistical analysis, and results. The assessments of statistical significance of the endpoints measured in the INCREASE trial (forced vital capacity ("FVC"), six minute walk distance ("6MWD"), N-terminal pro-brain natriuretic peptide ("NT-proBNP"), etc.) were based on comparisons of inhaled treprostinil to placebo.

34. The specification specifically states the following regarding INCREASE:

This study showed that among patients with pulmonary hypertension due to interstitial lung disease, treatment with inhaled treprostinil improved exercise capacity as shown by improvement in the 6-minute walk distance through the end of the 16-week treatment period. In addition, treatment with inhaled treprostinil was associated with a lower risk of clinical worsening than that with placebo, a reduction in NT-proBNP levels, and fewer exacerbations

of underlying lung disease. '327 patent at 36:45-53. The INCREASE study was the first time that a drug had been shown to successfully improve the exercise capacity of PH-ILD patients in a placebo-controlled, randomized clinical study.

35. The INCREASE data provided in the specification demonstrates that administration of treprostinil according to the claimed methods of administration in the '327 patent resulted in a statistically significant improvement of exercise capacity in PH-ILD patients as measured by the 6MWD test. The 6MWD results are presented in the specification and demonstrate that, in the aggregate, patients receiving inhaled treprostinil exhibited improvement at the first 6MWD measurement point and that improvement continued to grow steadily over the 16-week course of treatment. The 6MWD results also demonstrate that patients receiving placebo exhibited a gradual and continuing decline in 6MWD for the same 16-week course of treatment.

36. Additional data from INCREASE reported in the specification demonstrates that practicing the claimed methods results in fewer exacerbations and clinical worsening events, improvements in FVC, and reduced NT-proBNP levels in blood plasma.

37. The '327 patent issued from the '061 application, filed on April 16, 2021. The '061 application was filed with 23 claims, of which claim 1 was independent and the remainder were dependent claims. Claim 1 of the '061 application is replicated below:

1. A method of treating a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprising administering to a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of treprostinil, a prodrug thereof or a pharmaceutically acceptable salt thereof.

38. The first Information Disclosure Statement ("IDS") was submitted by counsel for UTC on May 12, 2021 and included U.S. Patent No. 10,716,793 (the "'793 patent") as well as "pilot studies [that] suggest that inhaled treprostinil can improve hemodynamics and functional



capacity in patients with Group 3 pulmonary hypertensions.” A second IDS was submitted by counsel for UTC on September 21, 2021.

39. On February 16, 2022, counsel for UTC filed a third IDS and a preliminary amendment that amended independent claim 1 to require an inhaled route of administration delivering at least 6 micrograms of treprostinil per breath. The third IDS listed multiple documents related to the clinical trial referenced by examples of the ’327 patent, Tyvaso® (treprostinil) Prescribing Information (2009) (the “2009 Tyvaso Label”), and the Petition for Inter Partes Review of the ’793 patent filed by Liquidia.

40. The United States Patent and Trademark Office (the “USPTO”) conducted a prior art search on August 21, 2022 on the “method of claim 1” and the names of the listed inventors, which returned 94 results. Some of these results include the ’793 patent, U.S. Patent Publication No. 2013/0096200 to Wade, et. al (“Wade ’200”), Kishan S. Parikh et al., *Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension*, 67 J. CARDIOVASCULAR PHARMACOLOGY 322 (2016) (unpublished manuscript) (“Parikh 2016”).

41. The examiner issued a non-final rejection on March 6, 2023 and, in doing so, indicated that they had considered all of the documents listed on the first, second, and third, IDS. In the non-final rejection, the examiner rejected all pending claims as anticipated by the below references:

- 42. Malinin et al. (WO2015/138423)
- 43. Zhang et al. (WO2016/205202)
- 44. Morgans et al. (WO2012/009097)
- 45. Wade et al. (WO2008/098196)
- 46. Bose et al. (WO2016/176399).

47. Counsel for UTC responded to the examiner's rejection on May 10, 2023, cancelling six of the dependent claims under examination and amending the remaining claims. Independent claim 1 was amended to strike "treating" and require an improvement in exercise capacity in PH-ILD patients, with additional requirements for the particular dose and titration of treprostinil administered by inhalation. The response also provided remarks as to why the amended claims were not anticipated by the references relied on by the examiner.

48. The examiner issued a notice of allowance on June 28, 2023, allowing all of the pending claims without further amendment.

49. During the prosecution of the '327 patent, the examiner expressly considered the following alleged prior art references:

50. The '793 patent was disclosed in the first IDS.

51. The 2009 Tyvaso Label was disclosed in the third IDS.

52. Version 23 of ClinicalTrials.gov Posting for "Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE" (NCT02630316) (Feb. 10, 2017) (the "2017 INCREASE Study Description") was disclosed in the third IDS.

53. M. Agarwal & A.B. Waxman, *Inhaled Treprostinil in Group-3 Pulmonary Hypertension*, 34 J. HEART LUNG TRANSPLANT S343 (2015) ("Agarwal 2015") was submitted to the USPTO in the first IDS.

54. Mariana Faria-Urbina et al., *Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease*, 196(2) Lung 139 (2018) ("Faria-Urbina 2018") was disclosed to the USPTO in the first IDS.

55. Wade '200 was disclosed to the USPTO in the third IDS.

**D. Person of Ordinary Skill in the Art**

56. The person of ordinary skill in the art ("POSA") to which the '327 patent is directed,

would have a graduate degree in medicine or a field relating to drug development, such as an M.D. or a Ph.D., with at least two years’ experience treating patients with interstitial lung disease (“ILD”), including with PH-ILD.

57. The POSA would be part of—and would consult with—a collaborative team, including with, e.g., a biostatistician and/or others having substantial experience with clinical trial design and interpretation.

58. UTC’s experts in this case, including Dr. Nathan, Dr. Wertheim, and Dr. Thisted, possess, at minimum, ordinary skill in art or experience and expertise with an adequate relationship to the asserted claims.

59. Dr. Nathan, Dr. Wertheim, and Dr. Thisted have worked alongside other professionals that possess or exceed the level of ordinary skill in the art and are able to provide opinions reflecting the perspective of the POSA.

#### **E. Relevant Claim Construction**

60. The preamble of claim 1 is “[a] method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising[.]” The parties have agreed that the preamble of claim 1 of the ’327 patent is limiting. A POSA would therefore read claim 1 as requiring the method of treatment to be performed with the intended purpose and expectation of improving exercise capacity in PH-ILD patients.

61. On October 21, 2024, the Court issued an order construing certain terms in the claims of the ’327 patent. The relevant constructions are below:

<b>Term</b>	<b>Court’s Construction</b>
“A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease” ’327 patent, claim 1	This preamble is limiting, as agreed by the parties
“a”/“the” in the following terms:	“one or more”

<p>“a patient,” “the patient,” “a maximum tolerated dose,” “a single administration event,” “the administering,” and “the single inhalation administration event”</p> <p>’327 patent, claims 1-5, 8-10, and 15-19</p>	
<p>“maximum tolerated dose”</p> <p>’327 patent, claim 1</p>	<p>plain and ordinary meaning; not indefinite</p>
<p>“pulsed inhalation device”</p> <p>’327 patent, claims 11 and 14</p>	<p>“a device that provides for non-continuous inhaled drug delivery”</p>

62. The remainder of the claim terms of the Asserted Claims are given their plain and ordinary meaning to the POSA at the time of the invention in light of the specification and prosecution history as understood within the technological field of the invention.

63. A POSA would interpret the Asserted Claims as requiring that the patients treated with inhaled treprostinil enjoy the required claimed benefits. A POSA would not interpret the Asserted Claims as requiring a measurement of the required endpoints. A POSA would understand that a benefit could result from the administration of inhaled treprostinil to their patient, because statistical significance was attained in a large, aggregated population of PH-ILD patients, even if they themselves did not take measurements and analyze the results in their own patient population.

## **F. Clinical Measurements Referenced in the Asserted Claims**

### **1. 6 Minute Walk Distance**

64. 6MWD is type of cardiopulmonary exercise test (“CPET”) that measures the distance a patient can walk in six minutes, without running or jogging.

### **2. NT-proBNP**

65. NT-proBNP is a protein that the body produces when the heart is dilated and under

stress. The concentration of NT-proBNP in a patient's blood plasma can be used as a measure of cardiac stress.

### **3. Exacerbations of Underlying Lung Disease**

66. The '327 patent defines "an exacerbation of underlying lung disease" as "an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality."

67. Exacerbations of underlying lung disease are typically associated with a significant, and often dangerous, decline in the functional health of PH-ILD patients that requires medical intervention.

### **4. Clinical Worsening**

68. The '327 patent defines a "clinical worsening event" as including one or more of the following: "hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death or a lung transplantation."

### **5. Forced Vital Capacity**

69. FVC is a type of pulmonary function test ("PFT") that measures the volume of air that a patient is able to exhale after inhaling as deeply as possible. FVC is measured as a single data point, but there are two expressions of FVC—absolute and percent predicted.

70. Absolute FVC is the raw measurement test results of the patient's FVC, which is reported in volumetric units, e.g., in liters or milliliters.

71. Percent predicted FVC compares the absolute volume to what a patient's optimal FVC (in volumetric units) should be, based on their demographics, and is ultimately reported as a percentage.

72. The demographic factors used to calculate percent predicted FVC include age, sex, height, arm span, and as of April 2020, race/ethnicity.

**G. Defendant's Knowledge of the '327 Patent and '061 Application**

73. Defendant has had knowledge of the '327 patent since at least November 15, 2023.

74. Defendant has had knowledge of the '061 application from which the '327 patent issued since at least June 29, 2023, the day after the '061 application received a notice of allowance from the USPTO.

**III. FACTUAL BACKGROUND ON THE SUBJECT MATTER OF THE '327 PATENT**

**A. Pulmonary Hypertension**

75. Pulmonary hypertension ("PH") is a disease state characterized by abnormally high blood pressure occurring in the pulmonary vasculature, blood vessels of the lungs including between the heart and lungs and occurs when there is a build-up of blood pressure in the pulmonary artery. PH is currently defined by a mean pulmonary artery pressure of greater than 20 mmHg.

76. Patients with PH often exhibit low blood oxygen saturation as result of an impaired ability to effect gas exchange in the lungs. This can cause a reduction in the patient's ability to move and exercise.

77. As of April 2020, a patient was considered to have PH if they exhibited a mean pulmonary arterial pressure ("mPAP") of 20 mmHg or greater.

78. PH is a heterogeneous clinical condition with many potential causes. As of April 2020, PH patients were commonly categorized as belonging to one of five different groups defined by the World Health Organization ("WHO Groups"), listed below:

- WHO Group 1 – Pulmonary Arterial Hypertension ("PAH") ("Group 1")
- WHO Group 2 – PH due to left heart disease ("Group 2")
- WHO Group 3 – PH due to lung disease ("Group 3")
- WHO Group 4 – PH due to pulmonary artery obstructions ("Group 4")
- WHO Group 5 – PH with unclear and/or multifactorial mechanisms ("Group 5")

79. WHO Group 1 is pulmonary arterial hypertension and is when the cause of the pressure build-up is from pathologic changes within the pulmonary artery and its tributaries, including the pulmonary arterioles which are further upstream and lead into the pulmonary capillaries. Medications and treatments for pulmonary hypertension are normally studied and approved for Group 1 PAH.

80. WHO Group 2 is pulmonary hypertension due to left-sided heart disease where a pressure build-up on the left side of the heart causes a pressure build-up in the pulmonary venous circulation that is then transmitted across the pulmonary capillaries and affects the pulmonary arterial side of the circulation. There are no pulmonary hypertension medications approved for Group 2 as treatment for Group 2 is usually aimed at treating the underlying heart disease.

81. WHO Group 3 pulmonary hypertension is caused by a buildup of pressure due to lung disease. There are two groups of lung disease ILD and chronic obstructive lung disease (“COPD”). ILD refers to a heterogenous group of conditions characterized by damage, inflammation, and/or scarring (fibrosis) to the lung parenchyma—the functional tissue of the lung responsible for gas exchange.

82. Unlike PH, which is diagnosed by a quantitative metric (mPAP), ILDs are diagnosed clinically through the use of medical imaging, laboratory testing, and/or pathology.

83. Idiopathic Interstitial Pneumonias (“IIPs”) make up the largest sub-category of ILDs, with idiopathic pulmonary fibrosis (“IPF”) being the most common form of IIP.

84. Patients with PH-ILD can be categorized based on their type of underlying ILD. For example, a PH-ILD patient suffering from IPF may be referred to as a “PH-IPF” patient.

85. Patients with PH-ILD have significantly reduced life expectancy as compared to patients with ILD alone. As of April 2020, the 5-year survival rate for patients with PH-ILD was

estimated to be approximately 14%, which is comparable to that observed in pancreatic cancer.

86. PH-ILD, pulmonary hypertension associated with ILD, has significant implications for morbidity and mortality with worse functional impairment, a greater need for supplemental oxygen, greater health care resource utilization, and a worse survival rate. There is a tendency to underdiagnose PH-ILD due to the similarity between PH-ILD and the underlying lung disease.

87. PH-ILD as a category refers to PH “due to” and “associated with” the patient’s ILD. Dr. Channick testified that “the very broad definition of PHILD is pulmonary hypertension that a clinician feels is due to the interstitial lung disease and not due to something else.” He also testified that:

Q. As part of your analysis in this case, what definition of PHILD did you apply?

A. My clinical diagnoses of PHILD was the definition that the patient has interstitial lung disease that I feel is causing pulmonary hypertension. If I have a patient like that, based on my 30 some years of experience, I make a determination -- and I don't find another cause for the pulmonary hypertension like illicit drug use or left sided heart disease or blood clots in the lungs, then I may make the diagnos[is] of [PHILD].

88. Dr. Wertheim confirmed Dr. Channick’s PH-ILD definition in his own testimony:

Q. Yep. Earlier you testified that PH-ILD, the way you referred to that was pulmonary hypertension due to interstitial lung disease, correct?

A. Due to, caused by. There’s a variety of ways of phrasing that.

Q. And it’s your opinion that PH-ILD is only limited to those cases in which the ILD is the cause for the pulmonary hypertension, correct?

A. It’s not only my opinion. It’s also the criteria set forth by the World Symposium of pulmonary hypertension.

Q. . . . Do you know whether pulmonary hypertension associated



with interstitial lung disease, as that term is used in the '327 patent, requires that the interstitial lung disease must be the driver of pulmonary hypertension?

A. Yes.

Q. You believe it does?

A. Yes.

Q. Okay. Do you believe that the pulmonary hypertension associated with interstitial lung disease, as that term is used in the '327 patent, requires that the extent of pulmonary hypertension is explained by ILD and no other factors?

A. Because that is the conventional understanding of what PH-ILD is, as defined by the guidelines that practitioners in the field commonly reference.

89. Dr. Nathan consistently defines PH-ILD:

Q. What did you understand the term "pulmonary hypertension associated with interstitial lung disease" to mean in the context of these claims in the '327 patent?

A. Pulmonary hypertension that is due to or caused by the interstitial lung disease. It's actually -- the way it's phrased, the best, most recent nomenclature for it is ILD and associated pulmonary hypertension, because invariably it's the ILD that comes first, followed by the pulmonary hypertension.

Q. So in your opinion, the ILD must be the cause of the pulmonary hypertension; is that correct?

A. Yes.

90. The presence of some ILD in a patient having PH does not always mean that the patient has PH-ILD (WHO Group 3). Patients with severe PH, out of proportion to the extent of their lung disease are often diagnosed as having Group 1 PAH. This determination comes down to whether the PH is severe enough or out of proportion to the lung disease enough that the physician determines that the PH was not due to the lung disease. Dr. Channick has testified concerning this

distinction between PAH and PH-ILD diagnoses:

It depends on the patient and whether we could have found other risk factors for PAH. I mean, I think that at the extremes it's kind of easy. Let me try to keep it simple here. If you had a patient with just a tiny bit of fibrosis, they had like, one or two little scars on their xray, but they had very, very severe Pulmonary Hypertension, and it was maybe somebody who fit profile of Idiopathic PAH, like a young woman with no other risk factors, I would probably call that group one, and in fact, those patients were included in group one studies that lead to approval of all these drugs. At the other extreme, again, it's pretty easy too. We still debate that middle ground. I can't give you like a set criteria for this patient, it's group 3, for this patient, it's group 1. It's just not -- it's a limitation of the classification system, as I'm sure you're learning.

91. Dr. Wertheim also testified concerning this distinction:

Q. . . . If a patient has pulmonary hypertension that is out of proportion to their interstitial lung disease, you would not consider than patient to have PH-ILD, correct?

A. I would consider them to have PAH, and that the ILD was an incidental phenomenon.

Q. So would that be an example of a type of patient who is a PAH patient with comorbid ILD?

A. Yes.

Q. Does pulmonary hypertension associated with interstitial lung disease, as that term is used in the '327 patent, include PAH patients with comorbid ILD?

A. No.

Q. And how do you know that?

A. Because PAH is a different pathophysiology than PH-ILD, which is a form of Group 3 pulmonary hypertension. And an expert in the field would not -- knows not to refer to PAH when -- when the ILD is the primary underlying driver of the pulmonary hypertension.

92. WHO Group 4 PH is caused by conditions that result in mechanical obstruction of the pulmonary vessels mostly through blood clots (pulmonary emboli) that fail to fully resolve and

result in obliteration and strictures (narrowing) of the pulmonary artery vessels. WHO Group 5 PH is caused by various miscellaneous conditions.

**B. Standard of Care in PH-ILD**

93. As of April 17, 2020, prognosis for patients diagnosed with PH-ILD was poor with a 5-year survival of approximately 14%, similar to the average life expectancy seen in pancreatic cancer.

94. A POSA would have understood that patients with PH complicating IPF have approximately 2-3 fold higher mortality rate than patient with IPF without PH and that the median survival of an IPF patient is approximately three years from the time of diagnosis.

95. As of April 17, 2020 there were no FDA- approved therapies for any Group 3 PH etiology meaning that patients received “supportive care” as well as referral for consideration of lung transplantation or heart-lung transplantation.

96. A POSA would have understood that faced with very ill patients and a lack of approved treatment options, clinicians treating PH-ILD prior to April 2020 sometimes resorted to prescribing drugs approved for Group 1 PH (PAH). Drugs targeting the nitric oxide pathway, such as the phosphodiesterase type 5 inhibitor (“PDE5i”) sildenafil, were most commonly used in this context. However, off-label use of Group 1 medications at this time was not supported by any placebo-controlled clinical data. Indeed international treatment guidelines gave Group 1 therapies no higher than a “class III” recommendation, which means that “treatment is not useful or effective and may be harmful.

97. A POSA would have understood from Gall H. *et al.*, *The Giessen Pulmonary Hypertension Registry: Survival In Pulmonary Hypertension Subgroups*, 36(9) J. Heart Lung Transplant 957 (2017) (“Gall 2017”) that the off-label use of prostanoids in Group 3 patients was uncommon:

	PAH	PVH	LD-PH <sup>b</sup>	CTEPH
Complete data, <i>n</i>	510	83	357	310
Initial monotherapy, <i>n</i> (%)				
PDE5i	170 (33)	29 (35)	209 (59)	200 (65)
ERA	102 (20)	1 (1)	36 (10)	12 (4)
IP	86 (17)	—	11 (3)	17 (6)
Other	8 (2)	—	1 (0)	2 (1)
Initial combination therapy, <i>n</i> (%)				
PDE5i + ERA	37 (7)	2 (2)	15 (4)	16 (5)
PDE5i + IP	21 (4)	1 (1)	4 (1)	7 (2)
Other	16 (3)	—	1 (0)	—
Triple therapy, <i>n</i> (%)	12 (2)	—	—	2 (1)
No specific therapy, <i>n</i> (%)	58 (11)	50 (60)	80 (22)	54 (17)

CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin-receptor antagonist; LD-PH, pulmonary hypertension due to lung disease; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type-5 inhibitor; IP, inhalative prostacyclins; PVH, pulmonary hypertension due to left heart disease.

<sup>a</sup>Data are presented as absolute numbers and percent of patients with complete data on drug use. During right heart catheterization, the patients were offered a PAH drug challenge to assess the acute effect of the drug on pulmonary and systemic hemodynamics and gas exchange.

<sup>b</sup>Treatment decisions were made on a patient-by-patient basis, referring to the criteria listed in the 2011 Cologne Consensus Conference<sup>41</sup> for the presence of severe pulmonary hypertension in patients with chronic lung disease (at least 2 of the following: mean pulmonary arterial pressure > 35 mm Hg; mean pulmonary arterial pressure ≥ 25 mm Hg with cardiac index < 2.0 liters/min/m<sup>2</sup>; and pulmonary vascular resistance > 480 dyne.s/cm<sup>5</sup>).

98. A POSA would have understood from Hoeper M.M. *et al.*, *Pulmonary Hypertension in Patients with Chronic Fibrosing Idiopathic Interstitial Pneumonias* 10(12) PLoS One e0141911 (2015) (“Hoeper 2015”) that off-label use of FDA approved PAH therapies in PH-ILD patients were either harmful or did not have significant benefits. In this study, of the 151 PH-ILD (PH-IIP) patients analyzed, just one received any form of prostacyclin therapy.

99. A POSA would have understood from the below listed references that PDE5i medications were the most common Group 1 therapy prescribed off label in Group 3:

- Rao R. *et al.*, Sildenafil Improves Six-minute Walk Distance in Chronic Obstructive Pulmonary Disease: A Randomised, Double-blind, Placebo-controlled Trial, 53 IND. J. CHEST DIS. & ALLIED SCI. (2011) (“Rao 2011”).
- Blanco, I., *et al.*, Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial, 42(4) EUR. RESPIR. J. 982 (2013) (“Blanco 2013”).
- Vitulo P. *et al.*, Sildenafil in Severe Pulmonary Hypertension Associated With Chronic Obstructive Pulmonary Disease: A Randomized Controlled Multicenter Clinical Trial, 36(2) J. HEART & LUNG TRANSPL. (2017) (“Vitulo 2016”).
- NCT03185364 Clinical Trial (June 14, 2017),

<https://clinicaltrials.gov/study/NCT03185364?term=NCT03185364&rank=1> (“2017 NCT03185364 Study Description”).

- Han M. et al., Sildenafil Preserves Exercise Capacity in Patients With Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction, 143(6) CHEST (2013) (“Han 2013”).
- Goudie A. et al., Tadalafil in patients with chronic obstructive pulmonary disease: a randomized, double-blind, parallel-group, placebo-controlled trial, (2) LANCET RESPIR. MED. (2014) (“Goudie 2014”).

100. A POSA would have understood that in order to obtain insurance coverage when prescribing a Group 1 therapy to a patient with symptoms of both PH and ILD, insurance companies would typically require that the patient had “PAH out of proportion” to their ILD—i.e., had a predominantly Group 1 phenotype rather than a Group 3 phenotype.

101. A POSA would have understood that a clinician would not attest that the patient had “PAH out of proportion” to their ILD unless the clinician believed that a Group 1 diagnosis was appropriate.

102. A POSA’s prescribing strategies as of April 17, 2020 would have been informed by Table 1 of Nathan S.D., *et al.*, *Pulmonary hypertension in chronic lung disease and hypoxia*, 53 EUR. RESPIR. J. 1801914 (2019) (Nathan 2019a):

TABLE 1 Criteria favouring group 1 versus group 3 pulmonary hypertension (PH)<sup>#</sup>

Criteria favouring group 1 (PAH)	Testing	Criteria favouring group 3 (PH due to lung disease)
<b>Extent of lung disease</b>		
Normal or mildly impaired: <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &gt;60% pred (COPD)</li> <li>• FVC &gt;70% pred (IPF)</li> <li>• Low diffusion capacity in relation to obstructive/restrictive changes</li> </ul>	Pulmonary function testing	Moderate to very severely impaired: <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt;60% pred (COPD)</li> <li>• FVC &lt;70% pred (IPF)</li> <li>• Diffusion capacity "corresponds" to obstructive/restrictive changes</li> </ul>
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan <sup>¶</sup>	Characteristic airway and/or parenchymal abnormalities
<b>Haemodynamic profile</b>		
Moderate-to-severe PH	Right heart catheterisation Echocardiogram	Mild-to-moderate PH
<b>Ancillary testing</b>		
Present	Further PAH risk factors (e.g. HIV, connective tissue disease, BMPR2 mutations, etc.)	Absent
Features of exhausted circulatory reserve: <ul style="list-style-type: none"> <li>• Preserved breathing reserve</li> <li>• Reduced oxygen pulse</li> <li>• Low CO/V<sub>O<sub>2</sub></sub> slope</li> <li>• Mixed venous oxygen saturation at lower limit</li> <li>• No change or decrease in P<sub>aCO<sub>2</sub></sub> during exercise</li> </ul>	Cardiopulmonary exercise test*  (P <sub>aCO<sub>2</sub></sub> particularly relevant in COPD)	Features of exhausted ventilatory reserve: <ul style="list-style-type: none"> <li>• Reduced breathing reserve</li> <li>• Normal oxygen pulse</li> <li>• Normal CO/V<sub>O<sub>2</sub></sub> slope</li> <li>• Mixed venous oxygen saturation above lower limit</li> <li>• Increase in P<sub>aCO<sub>2</sub></sub> during exercise</li> </ul>
Predominant haemodynamic profile		Predominant obstructive/restrictive profile

PAH: pulmonary arterial hypertension; FEV<sub>1</sub>: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; CT: computed tomography; BMPR2: bone morphogenetic protein receptor type 2; CO: cardiac output; V<sub>O<sub>2</sub></sub>: oxygen uptake; P<sub>aCO<sub>2</sub></sub>: arterial carbon dioxide tension. <sup>#</sup>: group 2 and 4 patients are excluded based on the diagnostic criteria of these groups; <sup>¶</sup>: parenchymal changes linked to pulmonary veno-occlusive disease may be discriminated from those associated with diffuse parenchymal lung diseases; \*: features of a limited circulatory reserve may be noted in severe COPD-PH and severe IPF-PH.

103. As of April 17, 2020, a POSA would not have been motivated by studies such as Rajeev Sagar et al., Changes in Right Heart Haemodynamics and Echocardiographic Function in an Advanced Phenotype of Pulmonary Hypertension and Right Heart Dysfunction Associated With Pulmonary Fibrosis, 69 THORAX 123 (2014) ("Sagar 2014"), Agarwal 2015, Parikh 2016, or Faria-Urbina 2018 to prescribe inhaled treprostinil to PH-ILD patients off-label.

104. A POSA would have understood that the standard of care in treating PH-ILD changed in 2021 when the results of UTC's INCREASE study were published, as INCREASE was the first placebo-controlled study in which a drug was shown to have a positive clinical benefit in Group 3 PH patients.

### C. Prior Failed Studies in Group 3 PH

105. As of April 17, 2020, there had been a number of attempts to determine whether medications approved for Group 1 PAH might also show efficacy in Group 3 PH patients with

lung disease. These efforts, however, frequently met with failure. Prior to UTC's successful INCREASE study with treprostinil, the results of which were first published in January 2021, not a single medication approved to treat Group 1 PAH had been shown to be safe and efficacious in Group 3 PH patients when subjected to rigorous clinical study.

106. Many hypotheses of potential crossover efficacy between Group 1 and Group 3 were based on retrospective, small-series, open-label and/or single-center studies. However, prior to INCREASE, all these hypotheses failed when investigated in larger, more reliable trials. The only way to know with a reasonable degree of scientific certainty whether a drug works is through prospectively designed, double-blind, randomized, placebo-controlled trials ("RCT"s)—the only types of studies the FDA will evaluate to consider drug approvals. This has resulted in many instances of drugs with alleged promise through less robust studies not panning out when subjected to controlled clinical trials.

107. The consistent failure of Group 1 drugs in Group 3 patients was well-publicized and created significant doubts in the field as to whether Group 1 therapies could ever be proven effective in PH-ILD and other Group 3 indications. These concerns are reflected in the literature, expert opinions, and guidelines published in the years leading up to April 17, 2020.

108. In reviewing medical literature on the use of PAH-specific medications to treat WHO Group 3 PH prior to April 17, 2020, a POSA would be struck by ambiguity in datasets and an overall sense of therapeutic nihilism—especially for PH-ILD generally and PH-IIP specifically. In 2019, one editorialist asked if identifying effective pharmacotherapy for PH-IIP was "an impossible dream."

109. POSA would have understood from the available literature on the use of PAH-specific therapies in ILD and in PH-ILD that it is not valid to consider PH-ILD only as a form of

pulmonary hypertension. Rather, it is a disease of PH and ILD, whereby events that occur in the lung parenchyma have bearing on patient outcomes. Indeed, if PH-ILD was only another form of pulmonary vasculopathy, one would expect that the patients with the most severe PH would have derived the greatest benefit from the studies in the prior art. Yet they did not. One would have also expected that sildenafil, bosentan, ambrisentan, macitentan, and riociguat would clearly show safety and efficacy in randomized, placebo-controlled trials. Yet they did not.

110. The efficacy of inhaled treprostinil and other PAH-specific medications was far from self-evident until the disclosure of data from the INCREASE trial. By the time of the results of the INCREASE study, many POSAs believed that no drug could be effective in improving exercise capacity in PH-ILD patients and seriously entertained the possibility that PH-ILD was an adaptive phenomenon, such that a patient could possibly be harmed if they were treated with PAH drugs.

111. A POSA would not have expected medications approved for PAH to be effective in Group 3 PH patients based on the ACTIVE Study (ClinicalTrials.gov ID No. NCT00109681) that found no significant differences between patients treated with iloprost and placebo.

112. A POSA would not have expected medications approved for PAH to be effective in Group 3 PH patients based on the STEP-IPF study (ClinicalTrials.gov ID No. NCT00517933) that found that sildenafil did not cause a significant difference in the proportion of patients with an improvement of 20% or more in 6MWD at 12 weeks after a number of pilot studies with positive 6MWD data.

113. A POSA would not have expected medications approved for PAH to be effective in Group 3 PH patients based on the BPHIT Study (ClinicalTrials.gov ID No. NCT00637065) that found that bosentan (which is approved for Group 1 PAH) resulted in no difference in pulmonary



hemodynamics, functional capacity, or symptoms between the bosentan and placebo patient groups over 16 weeks.

114. A POSA would not have expected medications approved for PAH to be effective in Group 3 PH patients based on the INSTAGE Study (ClinicalTrials.gov ID No. NCT02802345), which found that nintedanib (approved for the treatment of IPF) in combination with sildenafil did not provide a statistically significant benefit as compared to nintedanib alone.

115. A POSA would not have expected medications approved for PAH to be effective in Group 3 PH patients based on the RISE-IIP Study (ClinicalTrials.gov ID No. NCT02138825) which was terminated early because oral riociguat caused harm in the active treatment of patients, with more deaths, adverse events, and hospitalizations in the group receiving riociguat when compared to placebo. The RISE-IIP Study was conducted after a previous pilot study had also shown that oral riociguat improved 6MWD, cardiac output, and pulmonary vascular resistance in patients with PH-ILD.

116. A POSA would not have expected medications approved for PAH to be effective in Group 3 PH patients based on the PERFECT study (ClinicalTrials.gov ID No. NCT03496623), a UTC study based on treating PH-COPD patients with inhaled treprostinil, which failed despite inhaled treprostinil also showing promise for this indication in preliminary studies.

117. In view of the many negative trials and the widespread industry skepticism, a POSA would have been unlikely to use Tyvaso off-label to treat PH-ILD patients for the purpose or with the expectation of increasing exercise capacity.

118. “On May 20, 2023, Liquidia Corporation conducted a 4-hour advisory board in Washington, DC.” During this meeting Dr. Rahaghi, discussing several earlier trials that evaluated oral PAH therapies to treat PH-ILD and failed or were terminated early, stated, “[n]one of this

stuff really worked, and so this created a kind of nihilism on the part of the community’ of ILD physicians, he said of oral agents such as sildenafil, bosentan, ambrisentan, and riociguat.”

119. Liquidia’s September 2024 presentation titled, “PH-ILD Screening, Diagnoses, and Future Research” recognizes that many other manufacturers and researchers had tried and failed to develop a drug that was safe and effective to treat PH-ILD before the INCREASE study results finally showed that inhaled treprostinil could be a safe and effective treatment option for PH-ILD patients.

120. In June 2017, Rajeev and Rajan Saggarr provided UTC with a presentation they had prepared in an effort to convince UTC to initiate a PH-PF study using parenteral treprostinil, which contained information indicating that many other manufacturers and researchers had tried and failed to develop a safe and effective drug to treat PH-ILD.

121. The RISE-IIP study and the publication of its results heralded the peak of pessimism for treating PH-ILD. The RISE-IIP study indicated that treatments approved for PAH could be harmful for Group 3 PH patients.

122. Lewis J. Rubin, a named inventor of the ’793 patent, attended a large plenary session of the European Respiratory Society about the RISE-IIP study where he said “everyone knows that treating pulmonary hypertension associated with lung disease does not work.”

123. A POSA would have understood that not all drug compounds are appropriate for the treatment of PH-ILD based on the Sildenafil with Pirfenidone Study (ClinicalTrials.gov ID No. NCT02951429) which found that the addition of sildenafil to pirfenidone did not provide a treatment benefit when compared to placebo and was conducted after a pilot study showed promising results for the drug combination.

124. A POSA would have understood that not all drug compounds are appropriate for

the treatment of PH-ILD based on the PERFECT Study (ClinicalTrials.gov ID No. NCT03496623) which was terminated after treatment with treprostinil suggested potential harm to patients in the treatment group without any sign of benefit. The PERFECT Study was conducted after the publication of multiple positive hypothesis-generating reports, including Agarwal 2015 and Faria-Urbina 2018.

125. A POSA would have understood that not all drug compounds are appropriate for the treatment of PH-ILD based on the ARTEMIS-IPF Study (ClinicalTrials.gov ID No. NCT00768300) which was terminated after the treatment with ambrisentan showed a low likelihood of efficacy for the primary endpoint, median time to death or disease progression.

126. A POSA would have understood that not all drug compounds are appropriate for the treatment of PH-ILD based on the BUILD 3 Study (ClinicalTrials.gov ID No. NCT00391443) that found that there was no significant difference between patients treated with bosentan.

127. POSA would have understood that not all drug compounds are appropriate for the treatment of PH-ILD based on the MELODY-1 Study (ClinicalTrials.gov ID No. NCT02070991) which found that administration of macitentan resulted in significant fluid retention, increased adverse events and serious adverse events, and a non-significant change in NT-proBNP.

128. A POSA would have understood the risks of relying on uncontrolled, observational data based on the initially promising, yet failed PANTHER-IPF trial (Raghu G. *et al.*, *Prednisone, Azathioprine, and N-Acetylcysteine For Pulmonary Fibrosis*, 366(21) N. Engl. J. Med. 1968 (2012)).

129. A POSA would have understood the risks of relying on uncontrolled, observational data based on the initially promising BUILD-1 trial (King T.E. Jr. *et al.*, *BUILD-1: A Randomized Placebo-Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis* 177(1) Am. J. Respir.

Crit. Care Med. 75 (2008)), which was subsequently refuted by the BUILD-3 (King T.E. Jr., *et al.*, *BUILD-3: A Randomized, Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis*, 184(1) Am. J. Respir. Crit. Care Med 92 (2011)), MUSIC (Raghu G. *et al.*, *Macitentan For the Treatment of Idiopathic Pulmonary Fibrosis: the Randomised Controlled MUSIC Trial*, 42(6) Eur. Respir. J. 1622 (2013)), and ARTEMIS-IPF (Raghu G. *et al.*, *Treatment of Idiopathic Pulmonary Fibrosis With Ambrisentan: A Parallel, Randomized Trial*, 158(9) Ann. Intern. Med. 641 (2013)) trials.

130. A POSA would have understood the risks of relying on FDA approved therapies indicated for PAH for use in treating PH-ILD patients based on the STEP-IPF trial (Zisman D. *et al.*, *A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis*, 363(7) N Engl Med 620 (2010)).

131. A POSA would have understood the risks of relying on FDA approved therapies indicated for PAH for use in treating PH-ILD patients based on the BPHIT study (Corte T.J. *et al.*, *Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia*, 190(2) Am. J. Respir. Crit. Care Med. (2014)).

132. A POSA would have understood the risks of relying on FDA approved therapies indicated for PAH for use in treating PH-ILD patients based on the RISE-IIP study (Nathan S.D. *et al.*, *Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study*, 7(9) Lancet Respir Med. (2019)).

133. A POSA would have understood the risks of relying on FDA approved therapies indicated for PAH for use in treating PH-ILD patients based on the below references:

- Prins K.W. *et al.*, *Chronic Use of PAH-Specific Therapy in World Health Organization Group III Pulmonary Hypertension: A Systematic Review and Meta-Analysis*, 7(1) Pulm. Circ. 145 (2017) (“Prins 2017”).

- Harari S., *RISE-IIP: Some Pitfalls and Observations*, 7(11) Lancet Respir Med. E35 (2019) (“Harrari 2019”).
- Nathan S.D., *et al.*, *Pulmonary hypertension in chronic lung disease and hypoxia*, 53 Eur. Respir. J. 1801914 (2019) (“Nathan 2019a”).
- Raghu G., *Idiopathic Pulmonary Fibrosis: Lessons from Clinical Trials Over the Past 25 Years*, 50(4) Eur. Respir. J. 1701209 (2017) (“Raghu 2017”).
- Maron B.A. & Ryan J.J., *A Concerning Trend for Patients with Pulmonary Hypertension in the Era of Evidence-Based Medicine*, 139(16) 1861 (2019) (“Maron & Ryan 2019”).

**D. Methods of Administration for Treating Pulmonary Hypertension**

134. There are about 14 medications that are approved to treat only Group 1 PAH, inhaled treprostinil which is approved to treat both Group 1 PAH and PH-ILD, and riociguat which is approved to treat Group 1 PAH and Group 4 chronic thromboembolic pulmonary hypertension (“CTEPH”). Each of these falls into one of four classes of agents (prostanoid, endothelin, nitric oxide, or activin), each of which targets a different biological pathway in the body. Treprostinil is a prostanoid.

135. Third party payors such as insurers typically require prior authorization before approving of payments for treprostinil as well as many of the other PH drugs. Development of Treprostinil to Treat PH-ILD Patients

136. Prior to the approval of Tyvaso® for PH-ILD in April 2021, there was no therapy that had been shown to improve exercise capacity in patients with PH-ILD. Tyvaso® was previously approved in July 2009 to treat Group 1 PAH.

137. Tyvaso® was approved because the INCREASE study demonstrated an improvement in exercise capacity manifested by a statistically significant increase in 6MWD.

INCREASE was the first randomized controlled clinical trial to evaluate the use of inhaled treprostinil in PH-ILD patients. The INCREASE study is titled “A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease.” The INCREASE study also resulted in a reduction in plasma concentration of NT-proBNP (an indicator of heart strain), fewer clinical worsening events, improvement in FVC, and a reduction in acute exacerbations.

138. The primary endpoint of the INCREASE study was change in 6MWD measured at peak exposure from baseline to week 16. The secondary endpoints of the INCREASE study were change in plasma concentration of NT-proBNP and time to clinical worsening. Statistical analyses of FVC and acute exacerbation of underlying lung disease were conducted post hoc.

139. Patients were selected for inclusion in the INCREASE study population based on exclusion and inclusion criteria. Patients were randomized to receive placebo or Tyvaso in 4 daily treatment sessions with a target dose of at least 9 breaths (54 mcg) per session and a maximum dose of 12 breaths (72 mcg) per session over the 16-week course of INCREASE.

140. The INCREASE study showed a statistically significant increase in 6MWD, reduction of plasma concentration of NT-proBNP, reduction of clinically worsening events, fewer acute exacerbations of disease, and improvement in the forced vital capacity.

#### **E. Hemodynamic Parameters and Functional Tests**

141. In designing phase 2 trials in PH and PH-ILD it is common to use a hemodynamic biomarker endpoint as a measure of the interaction between the drug compound and its intended biological target. Commonly-employed hemodynamic measures as of April 2020 included: pulmonary vascular resistance (“PVR”), pulmonary artery pressure (“PAP”), pulmonary artery wedge pressure (“PAWP”), central venous pressure (“CVP”), systemic vascular resistance

(“SVR”), systemic arterial pressure (“SAP”), central venous oxygen saturation (“SvO2”), arterial oxygen saturation (“SaO2”), and heart rate. PAP is the benchmark characteristic for determining if a patient has pulmonary hypertension. As of April 2020, patients having a mean PAP of 20 mmHg or higher were considered to have pulmonary hypertension.

142. 6MWD, clinical worsening, hospitalization, disease exacerbations, and death are commonly used functional endpoints in phase 3 PH studies. A POSA would recognize that 6MWD is the best standard test for demonstrating an improvement in exercise capacity in PH-ILD patients. FVC is a pulmonary function test that measures the volume of air that a patient can exhale after inhaling as deeply as possible and is commonly used as a primary endpoint in ILD studies. NT-proBNP can also be measured to indicated a patient’s function as a patient produces more NT-proBNP when the heart ventricles are under stress or increased pressure.

143. During a six-minute walk test, patients are asked to “walk as far as possible for 6 minutes” down back and forth down a hallway of at least 30 meters, without running or jogging, in accordance with the American Thoracic Society (“ATS”) guidelines. The total distance walked, i.e., the 6MWD, can be clinically prognostic. In the care of patients with PAH, 6MWD has been a mainstay of clinical trials aiming to test the efficacy of new treatments. Furthermore, 6MWD is included in commonly used PAH risk calculators and a decline in 6MWD is a predictor of mortality. In the context of ILDs, 6MWD can be predictive of mortality and clinical deterioration. 6MWD is also a required element of the algorithm that calculates a patient’s ranking on the lung transplantation list in the setting of end-stage lung diseases from PH, ILD, or other etiologies. 6MWD continues to be used commonly in patient care and clinical trials, likely owing to its simplicity, prognostic ability, and historical track record in pivotal phase 3 clinical trials.

144. When FVC is measured clinically, the resulting data is typically expressed in one

of two ways: “absolute FVC” and “percent predicted FVC.” Absolute FVC is the raw measurement from testing the patient and is reported in volume units (e.g., in liters or milliliters). Percent Predicted FVC compares this volume to what a patient’s optimal FVC should be based on their demographics and is reported as a percentage. The demographic factors used to calculate percent predicted FVC include age, sex, height, arm span, and as of April 2020, race/ethnicity. For example, if a patient is predicted by demographic factors to have a healthy FVC of 5.0 L, but actually records an absolute FVC value of 4.0 L, their percent predicted FVC value would be 80%—i.e., their absolute FVC measurement is 80% of what was predicted. Percent predicted FVC is particularly useful when comparing the data from multiple patients (e.g., in the context of a clinical trial), because it accounts for how lung physiology may vary across a population due to demographic factors. For example, a male who is 6’5” tall would not be expected to have the same absolute FVC as a female who is 5’1” tall, even if both have completely healthy lungs. The consequence of this is that the same change in absolute FVC may impact two patients differently depending on their underlying differences in lung physiology. Expressing FVC as a percent predicted value accounts for these differences so that the data from different patients can be more accurately compared.

**F. Drug Labels and their Influence on Administration**

145. Prescription medications sold in the United States are typically provided with a “package insert” that provides prescribing details about the drug as well as “instructions for use” that tells patients how to administer and use the drug. Healthcare providers typically refer to this collection of information as the drug’s “label.” In general, a drug’s label discloses important information to both physicians and patients concerning how to use the drug safely and effectively.

146. Healthcare providers would review, would be aware of, and would rely on the entirety of a drug’s label prior to prescribing, administering, or instructing a patient on self-



administration of a drug. This is the standard of care.

147. Reviewing and following the drug's label is the rule for healthcare providers, and not the exception. Healthcare providers rely upon the entirety of the drug's label when determining what drug to prescribe a patient to treat a given disease or condition, as well as to ensure proper administration of the drug.

148. Healthcare providers would review, or at least be aware of, a drug's label prior to prescribing a drug for the first time, and if necessary, would review information regarding the clinical trials cited in the label—including publications, abstracts, and/or presentations related to the clinical study results—to determine if the drug is suitable for their patients. This is standard practice and conforms with the standard of care physicians are expected to provide to their patients. Healthcare providers treating PAH and PH-ILD would conduct this due diligence before prescribing medications for these conditions. For example, before prescribing a drug for the first time, a healthcare provider may review the label in full, including, its “indications and usage,” “dosage and administration,” “dosage forms and strengths,” “adverse reactions,” and “clinical studies” sections.

149. Drug labels also include valuable information about the clinical trials that were used to obtain FDA approval for the medicine. The clinical studies section of drug labels does not provide an all-inclusive review of all of the study data available from a clinical study for a specific drug. As such, healthcare providers may expand their review of the cited clinical studies to include publications, abstracts, and/or presentations related to the clinical study results, to determine if the drug is suitable for their patients.

150. Because pulmonary hypertension can present in a wide variety of clinical contexts, it is especially important to review the cited clinical studies, including data available in

publications, abstracts, and/or presentations to ensure that the patient's condition or disease matches the condition or disease to which the clinical studies were directed. Drugs that effectively treat one group of PH do not necessarily effectively treat other groups or even other conditions within the same group. This makes a review of the cited clinical trials critical in determining the suitability of a drug for a particular patient.

151. When prescribing a drug for the treatment of PAH or PH-ILD, healthcare providers are careful to instruct patients to use the drug as the label directs. The first time healthcare providers prescribes an inhaled therapy like Tyvaso<sup>®</sup> to a PAH or PH-ILD patient they should review the label with the patient and instruct the patient how to use the required inhalation device. Specifically, they should make sure to review at least the portions of the label discussing the dosage and administration of the drug, the risks and benefits, and potential side effects with the patient.

152. Patients administer drugs according to their healthcare providers' orders.

153. A healthcare provider prescribing off-label does not have any supporting clinical data. A POSA would not prescribe a medication if they are aware of a study indicating harm.

#### **G. Principles of Clinical Study Design and Statistics**

154. Descriptive/single-arm clinical studies cannot determine whether some or all of the patient outcomes observed are a result of the treatment that the patients received, i.e., effectiveness cannot be determined. Single-arm clinical studies that rely on a change from baseline in a clinical performance measure are prone to bias because the natural course of the disease can change the outcome measures, other treatments being used simultaneously can be the cause of symptom reduction, and regression to the mean can occur.

155. FDA relies on adequate and well-controlled studies when determining whether there is substantial evidence to support a claim that a drug is effective. .

156. Retrospective clinical studies are based on data that are often inaccurate,

misleading, or incomplete. Selectively including patients with complete data sets for inclusion in retrospective clinical studies, and excluding those without complete data sets, introduces bias that can produce substantially misleading results. Prospective clinical studies are subject to fewer types of bias than retrospective clinical studies.

157. Blinding in a clinical study ensures that the treatment choices during the clinical study are unaffected by the treatment being studied.

158. Selection bias can be introduced to clinical studies when the inclusion and exclusion criteria filter out some or all patients with particular characteristics, only a subset of an initially representative study is analyzed, and patients receiving treatment differ in a systematic way from those receiving a control treatment.

159. Randomized clinical trials provide the best means for controlling for potential biases.

160. Clinical studies that are conducted a single specialty clinical may not be indicative of results obtainable in a broader range of clinical settings.

161. A clinical study that is properly powered will result in more precise results. Larger clinical studies generally have greater power.

162. Statistical significance occurs when the p-value is less than 0.05. P-values generated when analyzing nonrandomized or noncomparative clinical studies are merely descriptive measures that have no necessary relationship to the role of chance as a possible explanation of observed effects.

#### **IV. FACTS PERTAINING TO INFRINGEMENT OF THE '327 PATENT**

##### **A. Plaintiffs' Tyvaso<sup>®</sup> and Tyvaso DPI<sup>®</sup> Products**

163. Plaintiff markets and sells Tyvaso<sup>®</sup> (treprostinil) Inhalation Solution, 0.6 mg/ml, under the registered U.S. Trademark Tyvaso<sup>®</sup>.

164. Tyvaso<sup>®</sup> was initially approved by the FDA in the United States in July 2009. Tyvaso<sup>®</sup> was approved in 2009 as indicated for the treatment of pulmonary arterial hypertension (“PAH”). In 2021, Tyvaso<sup>®</sup> was approved as indicated for the treatment of pulmonary hypertension associated with interstitial lung disease.

165. Tyvaso<sup>®</sup> was the first medication ever to receive FDA approval for the treatment of PH-ILD or any other form of WHO Group 3 pulmonary hypertension.

166. Tyvaso<sup>®</sup> is an inhalable product approved for sale in a 0.6 mg/ml concentration. Tyvaso<sup>®</sup> solution is placed into a nebulizer, aerosolized by the nebulizer, and inhaled by the patient.

167. The Patent-in-Suit is listed in connection with Tyvaso<sup>®</sup> in the Orange Book.

168. Plaintiff markets and sells Tyvaso DPI<sup>®</sup> (treprostinil) Inhalation Powder, under the registered U.S. Trademark Tyvaso DPI<sup>®</sup>.

169. Tyvaso DPI<sup>®</sup> was approved by the FDA in the United States in May 2022 as indicated for the treatment of both PAH and PH-ILD.

170. Tyvaso DPI<sup>®</sup> was the first dry powder formulation of treprostinil to receive final approval from FDA and to be marketed and sold in the United States.

171. Tyvaso DPI<sup>®</sup> is an inhalable product approved for sale in single-dose plastic cartridges in 5 strengths: 16 mcg, 32 mcg, 48 mcg, 64 mcg, and 80 mcg. Tyvaso DPI<sup>®</sup> cartridges are loaded into a Tyvaso DPI<sup>®</sup> Inhaler and inhaled by the patient.

172. The Patent-in-Suit is listed in connection with Tyvaso DPI<sup>®</sup> in the FDA’s Orange Book.

## **B. The INCREASE Study**

173. The INCREASE study was multicenter, randomized, double-blinded, placebo-controlled, Phase III clinical trial conducted between February 3, 2017 and August 30, 2019.

Plaintiff was the sponsor of the INCREASE study.

174. The INCREASE study evaluated the safety and efficacy of inhaled treprostinil in PH-ILD patients.

175. The INCREASE study supported the approval of Plaintiff's Tyvaso<sup>®</sup> and Tyvaso DPI<sup>®</sup> for the treatment of PH-ILD.

176. The results of the INCREASE study are detailed in a Clinical Study Report dated May 5, 2020 ("INCREASE Clinical Study Report"), which Plaintiff submitted to FDA.

177. Publications related to the INCREASE study include, among others, Waxman A, et. al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, N Engl J Med. 2021 Jan 28, 384(4):325-334 ("Waxman 2021") and Nathan SD, et. al., *Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study*, The Lancet. Respiratory medicine 2021, 9(11):1266-1274 ("Nathan 2021").

178. The results of the INCREASE study were first published in Waxman 2021 on January 28, 2021.

179. The INCREASE study's statistical analysis plan ("SAP"), finalized on 12 December 2019, describes in detail how each efficacy measure will be constructed from the data recorded on each patient's electronic case report form ("eCRF") and the specific statistical analysis to be carried out for each efficacy measure, and the SAP details how the statistical analyses relate to study objectives, characteristics of the study design, the sequence of planned analyses, sample size considerations, the populations to be analyzed, any interim analyses to be conducted, and general considerations for data analysis.

180. The INCREASE study's final prespecified efficacy and safety endpoints were as

follows:

<p><b>PRIMARY ENDPOINT</b></p> <ul style="list-style-type: none"> <li>The primary endpoint is the change in 6-minute walk distance measured at peak exposure from Baseline to Week 16.</li> </ul> <p><b>SECONDARY ENDPOINTS</b></p> <ul style="list-style-type: none"> <li>The secondary efficacy endpoints are (listed in hierarchical testing order): <ol style="list-style-type: none"> <li>Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16</li> <li>Time to clinical worsening calculated as the time from randomization until 1 of the following criteria are met: <ol style="list-style-type: none"> <li>Hospitalization due to a cardiopulmonary indication</li> <li>Decrease in 6-minute walk distance &gt;15% from Baseline directly related to disease under study, at 2 consecutive visits, and at least 24 hours apart</li> <li>Death (all causes)</li> <li>Lung transplantation</li> </ol> </li> <li>Change in peak 6-minute walk distance from Baseline to Week 12</li> <li>Change in trough 6-minute walk distance from Baseline to Week 15</li> </ol> </li> </ul> <p><b>EXPLORATORY ENDPOINTS</b></p> <ul style="list-style-type: none"> <li>Exploratory endpoints are (not included in hierarchical testing): <ol style="list-style-type: none"> <li>Change in peak 6-minute walk distance from Baseline to Week 4</li> <li>Change in peak 6-minute walk distance from Baseline to Week 8</li> <li>Change in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16</li> <li>Change in distance saturation product from Baseline to Week 16</li> </ol> </li> </ul> <p>Exploratory endpoints of optional evaluation are change in biomarkers from Baseline to Week 16, and optional evaluation of whole genome sequence. They are specified in separate documents and are not covered in the statistical analysis plan.</p> <p><b>SAFETY ENDPOINTS</b></p> <ul style="list-style-type: none"> <li>Safety endpoints are (not included in hierarchical testing): <ol style="list-style-type: none"> <li>Adverse events</li> <li>Oxygenation as measured by pulse oximetry (saturation of peripheral capillary oxygenation) and supplemental oxygen requirement (L/min)</li> <li>Pulmonary function tests, specifically: forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and lung diffusion capacity</li> <li>Clinical laboratory parameters</li> <li>Vital signs</li> <li>Electrocardiograms</li> <li>Hospitalizations due to a cardiopulmonary indication</li> <li>Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality</li> </ol> </li> </ul>
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181. The interstitial lung disease diagnosis of PH-ILD patients participating in the INCREASE study was confirmed using computed tomography scans of each patient's chest. These scans were reviewed by the principal investigator and a radiologist at each of the study centers.

182. The detailed statistical analyses of the INCREASE FVC and incidence of acute

exacerbation of the underlying lung disease results were not prespecified in the study protocol or statistical analysis plan, so they are “post-hoc.” These post-hoc analyses closely followed the analytical approach that had been adopted for the prespecified efficacy variables in the INCREASE study’s statistical analysis plan.

183. Defendant’s Proposed Label describes the patients enrolled in INCREASE as “predominantly ha[ving] etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%).”

184. The interstitial lung disease diagnosis of PH-ILD patients participating in the INCREASE study was confirmed using computed tomography of the chest. These HRCT scans were reviewed by the principal investigator and a radiologist at each of the study centers. Dr. Steven Nathan, a steering committee member of the INCREASE study, also confirmed the interstitial lung disease diagnosis by personally reviewing the HRCT scans of patients included in the INCREASE study.

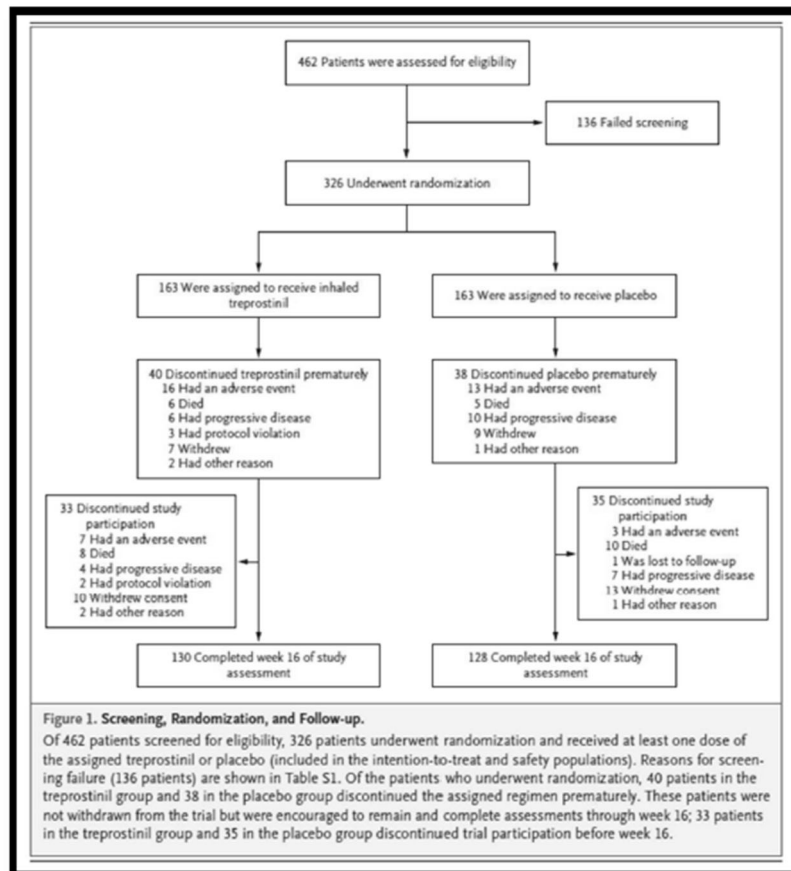
185. Pulmonary hypertension in each of the INCREASE study’s patients was confirmed by right heart catheterization. The INCREASE study defined Group 3 pulmonary hypertension as pulmonary vascular resistance of more than 3 Wood units, pulmonary capillary wedge pressure of 15 mm Hg or lower, and mean pulmonary arterial pressure of 25 mm Hg or higher.

186. The INCREASE study excluded any patient receiving an approved therapy for pulmonary arterial hypertension within 60 days before randomization, any patients who were taking drug treatments for their underlying lung disease if they were not receiving a stable dose for at least 30 days before randomization.

187. The INCREASE study’s 326 participants were equally randomized to be

administered active treatment (inhaled treprostinil) or placebo.

188. The disposition of the INCREASE study's subjects is illustrated by the following chart from Waxman 2021:



189. The final INCREASE trial protocol specified that inhaled treprostinil or placebo were administered by an ultrasonic pulsed-delivery nebulizer starting at 3 breaths, four times a day and was adjusted, with dose escalation (an additional 1 breath four times daily) occurring as often as every 3 days, with a target dose of 9 breaths four times daily and a maximum dose of 12 breaths four times daily, each breath comprising 6 µg of inhaled treprostinil.

190. The INCREASE study administered inhaled treprostinil at a concentration of 0.6 mg/mL corresponding to 6 µg per breath.

191. Inhaled treprostinil or placebo were administered by an ultrasonic pulsed-delivery



nebulizer starting at 3 breaths, four times a day and was adjusted, with dose escalation (an additional 1 breath four times daily) occurring as often as every 3 days, with a target dose of 9 breaths four times daily and a maximum dose of 12 breaths four times daily, each breath comprising 6 µg of inhaled treprostinil.

192. The INCREASE study dosed subjects as follows:

Once informed consent has been signed, all entry criteria have been met, and the randomized treatment assignment confirmed, the first dose of study drug (3 breaths; 18 mcg) will be inhaled in the clinic, followed by at least a 1 hour observation period (defined as Day 1). Study drug doses should be maximized throughout the study, dose escalations (additional 1 breath 4 times daily) can occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily within 4 weeks of beginning the treatment, as clinically tolerated. Table 6-1 provides a guideline for the recommended dose escalations.

**Table 6-1 Recommended Inhaled Treprostinil Dose Escalation Table**

Study Day*	Single Dose	Total Daily Dose
<b>Titration to maximum dose of 12 breaths</b>		
1-3	3 breaths QID (18 mcg)	72 mcg
4-6	4 breaths QID (24 mcg)	96 mcg
7-9	5 breaths QID (30 mcg)	120 mcg
10-12	6 breaths QID (36 mcg)	144 mcg
13-15	7 breaths QID (42 mcg)	168 mcg
16-18	8 breaths QID (48 mcg)	192 mcg
19-21	9 breaths QID (54 mcg)	216 mcg
22-24	10 breaths QID (60 mcg)	240 mcg
25-27	11 breaths QID (66 mcg)	264 mcg
28 (and beyond)	12 breaths QID (72 mcg)	288 mcg

Abbreviations: QID, 4 times daily; mcg., micrograms

\* Study day refers to the days on study drug with Day 1 referring to the first dose of study drug.

The dosing schedule is recommended as a guide only. The Investigator may determine the appropriate dosing schedule on an individual subject basis, considering tolerability and functional improvement.

If subjects are unable to tolerate the initial 3 breaths, they may decrease their next dose to 1 or 2 breaths of study drug (as determined by the Investigator) 4 times a day during waking hours. The subject will then gradually increase their dose to reach a minimum of 3 breaths, and titrate to a target dose of 9 breaths and a maximum dose of 12 breaths 4 times a day during waking hours, as clinically tolerated.

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. Telephone calls/emails between the site and subject should occur prior to each dose adjustment or at least weekly to monitor for AEs, clinical worsening events, and make decisions about dose titration.

193. The INCREASE study measured the following parameters on a fixed schedule throughout the duration of the study: 6MWD, plasma concentration of NT-proBNP, FVC, occurrence of clinical worsening events due to interstitial lung disease, and occurrence of exacerbations due to interstitial lung disease. 6MWD data were obtained at baseline and after 8, 12, and 16 weeks. NT-proBNP and FVC data were obtained at baseline and after 8 and 16 weeks.

194. The INCREASE study demonstrated that administration of inhaled treprostinil results in improved exercise capacity in PH-ILD patients, as evidenced by an increase in 6MWD.

195. The INCREASE study demonstrated a statistically significant increase in 6MWD in PH-ILD patients after 8 weeks, 12 weeks, or 16 weeks of the administering of inhaled treprostinil.

196. Mixed-Model Repeated Measures (“MMRM”) takes into account the fact that the measurements for each patient are correlated, and it allows for all data available for each patient to be used without the need for imputation of missing values.

197. Markov Chain Monte Carlo (“MCMC”) method estimates the difference in average change between treatment and placebo group, differing from MMRM primarily in how it handles missing data.

198. The INCREASE protocol prespecified that MCMC multiple imputation would be carried out as a sensitivity analysis of the primary efficacy variable, change in 6MWD.

199. The purpose of sensitivity analyses is to evaluate the robustness of findings to alternative statistical methods—when alternative statistical approaches to the same question produce similar answers—as they do in the INCREASE study—it increases confidence in the accuracy, reliability, and robustness of the results reported from the primary analysis.

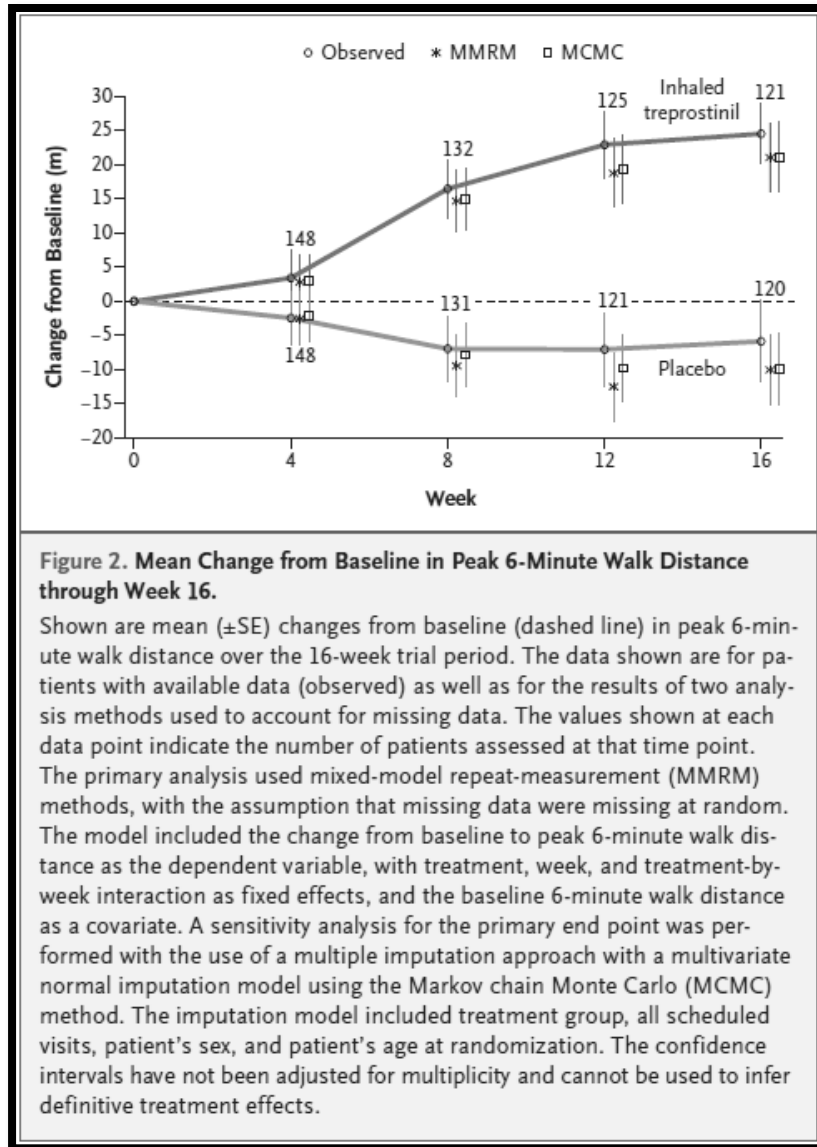
200. MMRM statistical methods were used to analyze treatment differences between

treatments in the change in 6MWD from baseline to Week 8, Week 12, and Week 16; and the specific model used, the steps taken to ensure that the model assumptions were satisfied, and the sensitivity analyses to check the robustness of the results are described in the Supplementary Appendix of Waxman 2021.

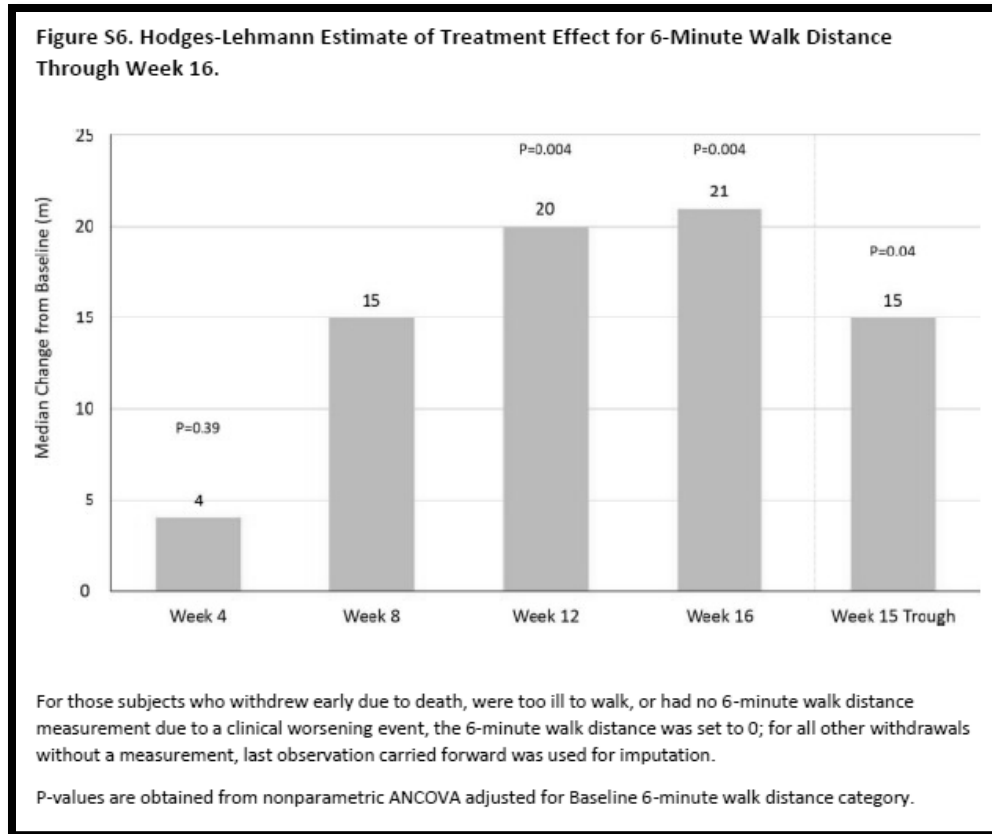
201. Waxman 2021 reports a statistically significant improvement in 6MWD after 12 and 16 weeks using MMRM analysis, reporting that the least squares mean difference between the treprostinil group and the placebo group in the change from baseline in peak 6-minute walk distance was 31.29 m and 31.12 m (95% confidence interval [CI], 17.37 to 45.21, 16.85 to 45.39;  $P < 0.001$ ,  $P < 0.001$ ), respectively (Table 2 and Fig. S1), which is the same data reported in Figure 4 of the '327 patent.

202. Waxman 2021 indicates a statistically significant improvement in 6MWD after 16 weeks using MCMC method, reporting that between-group difference in the change from baseline in peak 6-minute walk distance at week 16 was 30.97 m (95% CI, 16.53 to 45.41;  $P < 0.001$ ) (Fig. S3), which is the same data reported in Figure 6 of the '327 patent.

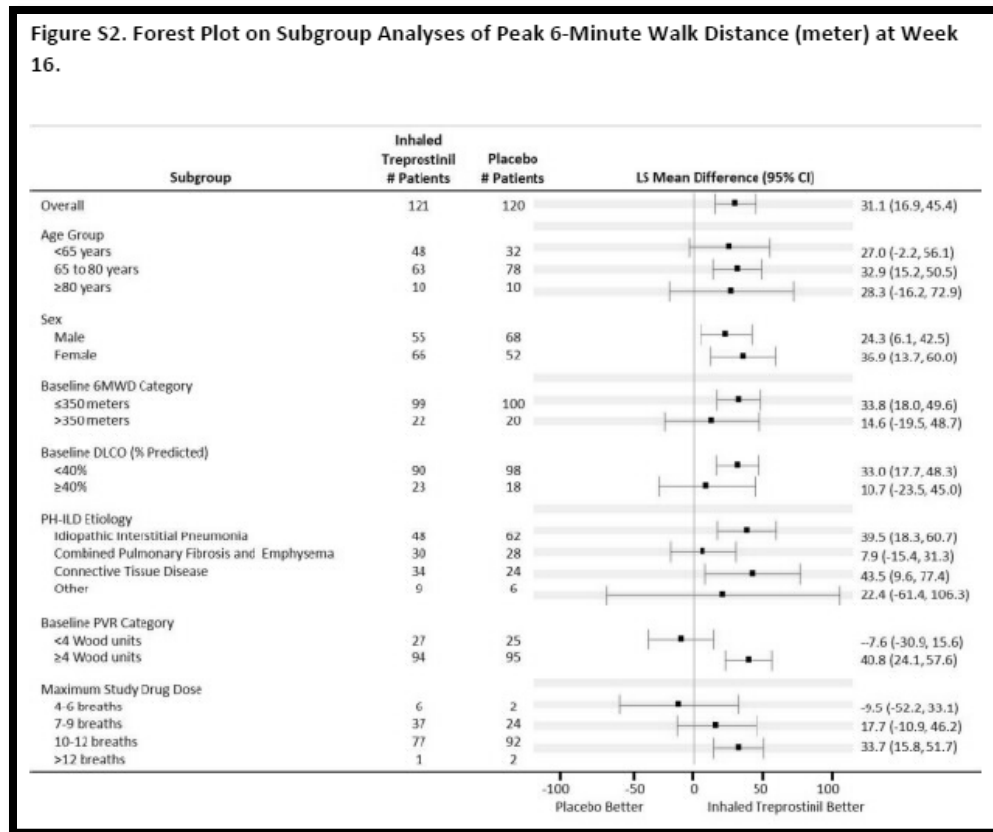
203. Figure 2 of Waxman 2021 reports observed, MMRM, and MCMC for mean change from baseline in 6MWD at 8, 12, and 16 weeks, which is the same data reported in Figure 3 of the '327 patent:



204. Figure S6 of Waxman 2021 reports Hodges-Lehmann estimate of treatment effect for 6MWD at 8, 12, and 16 weeks, which is the same data reported in Figure 8 of the '327 patent and Figure 3 of the Yutrepia™ label:



205. Figure S2 of Waxman 2021 reports subgroup data for 6MWD at week 16, which is the same data in Figure 4 of the Yutrepia™ label:



206. The INCREASE Clinical Study Report reports increases between treprostinil and placebo in peak 6MWD at Week 8 (15.0 m;  $p=0.0104$ ), Week 12 (20.0 m;  $p=0.0041$ ), and Week 16 (21.0 m;  $p=0.0043$ ).

207. Table 11-9 of the INCREASE Clinical Study Report reports statistically significant improvements in 6MWD after 8 weeks ( $p=0.0002$ ) and 12 weeks ( $p<0.0001$ ) using MMRM:

Visit	Treatment	N	LS Mean	Estimated Difference	95% CI	p-value
Week 8	Inhaled Treprostinil	132	14.69	24.13	11.48, 36.79	0.0002
	Placebo	131	-9.45			
Week 12	Inhaled Treprostinil	125	18.77	31.29	17.37, 45.21	<0.0001
	Placebo	121	-12.52			

Abbreviations: 6MWD, 6-Minute Walk Distance; CI, confidence interval; ITT, Intent-to-Treat; LS, least square; MMRM, mixed model repeated measurement

Note: LS mean, p-values, estimated difference, and its 95% CI were from the MMRM with the change from Baseline in peak 6MWD as the dependent variable; treatment, week, and treatment by week interaction as the fixed effects; Baseline 6MWD as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Source: Table 14.2.1.8

208. The INCREASE study demonstrated an increase in 6MWD of PH-ILD patients by

at least 10 m after 8 weeks, 12 weeks, and 16 weeks of the administering of inhaled treprostinil.

209. The INCREASE study demonstrated an increase in 6MWD of PH-ILD patients by at least 15 m after 12 weeks and 16 weeks of the administering.

210. The INCREASE study demonstrated a statistically significant reduction of a plasma concentration of NT-proBNP in PH-ILD patients after 8, 12, or 16 weeks of the administering of inhaled treprostinil.

211. Biological measurements may have highly skewed distributions, with much more variability in high values than in low values, and typically by taking the logarithm of such values (the log-transformed data) the resulting distribution is much better described by a normal (Gaussian) bell-shaped distribution, which is a context in which many statistical methods work well. This is why the analysis of such variables is often carried out on the log-transformed data, and the results then transformed back to the original scale for purposes of description of the results.

212. Least-squares means are the group means after controlling for baseline, and are expressed as the estimated group mean for individuals whose baseline is at the average baseline value.

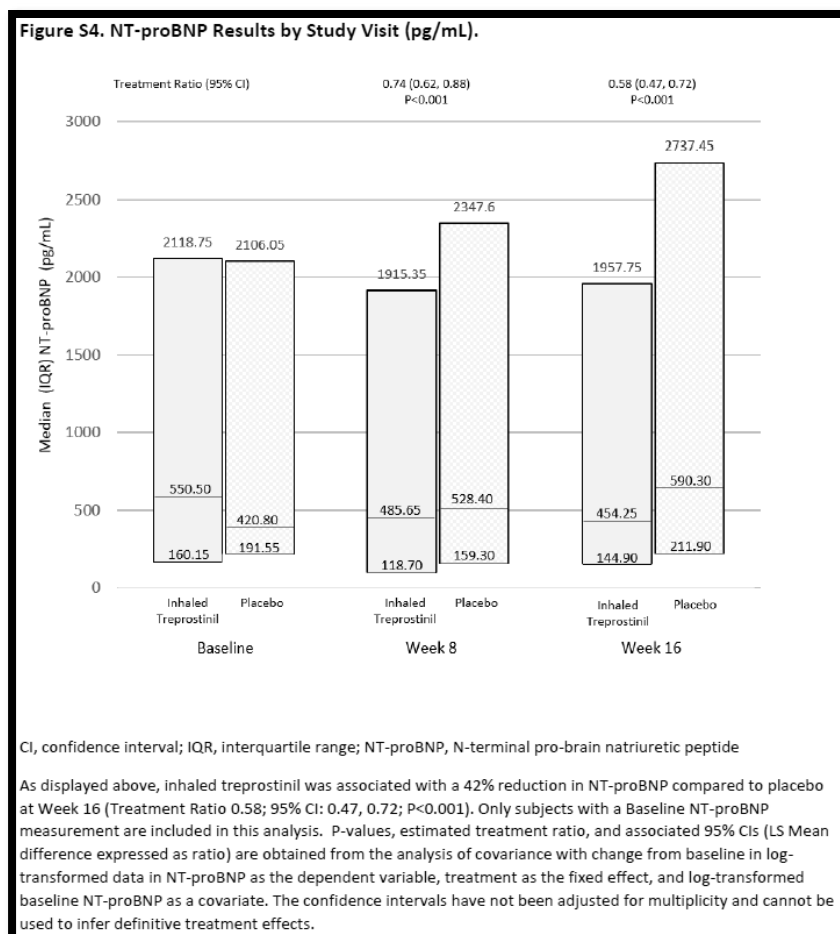
213. The statistical methods in the INCREASE study all included baseline values as covariates, recognizing the fact that patients with higher values at baseline also tend to have higher values at later time points, regardless of treatment, and the INCREASE statistical analysis controls for this effect, ensuring that it won't interfere with assessment of the treatment effect.

214. The Table 2 and Figure S4 of Waxman 2021 report the plasma NT-proBNP level decreased 15% from baseline with inhaled treprostinil and increased 46% from baseline with placebo, as assessed by the least-squares mean for the log-transformed ratio to the baseline level at week 16 (treatment ratio, 0.58; 95% CI, 0.47 to 0.72;  $P < 0.001$ ) and report mean change in NT-



proBNP levels from baseline after 16 weeks for inhaled treprostinil was -396.35 pg/ml while the mean change in NT-proBNP levels from baseline after 16 weeks for placebo group was 1453.95 pg/ml, and corresponds to the data in Figure 7 and Table 5 of the '327 patent:

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
<b>Secondary end points†</b>				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	-396.35±1904.90	1453.95±7296.20		
Median — pg/ml	-22.65	20.65		
Range — pg/ml	-11,433.0 to 5373.1	-5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)	<0.001
§ The effect of inhaled treprostinil as compared with placebo on the change in log-transformed NT-proBNP was evaluated with the use of a mixed-model repeat measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. Ratio to baseline is the least-squares mean of the change from baseline in log-transformed data. ¶ The change in plasma concentration of NT-proBNP from baseline to week 16 was assessed in 156 patients in the treprostinil group and 160 in the placebo group.    This is the treatment ratio, which is the ratio of ratios between two treatment groups.				



215. Table 11-6 of the INCREASE Clinical Study Report reports the same statistically significant NT-proBNP reduction data at week 8 and week 16:

<b>Visit</b>	<b>Treatment</b>	<b>N</b>	<b>LS Mean</b>	<b>Contrast</b>	<b>Estimated Difference</b>	<b>95% CI</b>	<b>p-value</b>
<b>Week 8</b>	Inhaled Treprostinil	145	0.82	Inhaled Treprostinil - Placebo	0.74	0.62, 0.88	0.0007
	Placebo	140	1.12				
<b>Week 16</b>	Inhaled Treprostinil	123	0.85	Inhaled Treprostinil - Placebo	0.58	0.47, 0.72	<0.0001
	Placebo	127	1.46				

Abbreviations: CI, confidence interval; ITT, Intent-to-Treat; LS, least square; MMRM, mixed model repeated measurement; NT-proBNP, N-terminal pro-brain natriuretic peptide

Note: LS mean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from Baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment by week interaction as the fixed effects; and log-transformed Baseline NT-proBNP as the covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Source: Table 14.2.2.5

216. Table 11-5 of the INCREASE Clinical Study Report reports statistically significant (p=0.0005) NT-proBNP data at Week 8 and reports the mean change in NT-proBNP levels from baseline after 8 weeks for the inhaled treprostinil group was -480.81 pg/ml while the mean change

in NT-proBNP levels from baseline after 8 weeks for the placebo group was 604.05 pg/ml:

Visit and Statistics	Inhaled Treprostinil N=163		Placebo N=163		p-value*
	Value	Change from Baseline	Value	Change from Baseline	
Week 8					
n	156	156	160	160	–
Mean (SD)	1376.72 (2099.32)	-480.81 (1659.28)	2412.91 (4841.95)	604.05 (3220.46)	–
Geometric mean (geometric SD)	481.00 (4.86)	–	601.23 (5.71)	–	–
Median	485.65	-11.25	528.40	0.00	–
Interquartile	118.70, 1915.35	-469.95, 42.40	159.30, 2347.60	-52.33, 317.40	–
Min, Max	10.2, 13,797.0	-9704.2, 3757.0	10.2, 40,511.0	-5483.3, 34,807.3	–
LS mean (SE)	–	0.8319 (1.05862)	–	1.1027 (1.05786)	0.0005
LS mean difference (SE)	–	0.7545 (1.08336)	–	–	–
95% CI of LS mean difference	–	(0.6445, 0.8832)	–	–	–

217. The INCREASE study demonstrated a reduction of a plasma concentration of NT-proBNP in PH-ILD patients by at least 200 pg/mL after 8 weeks, 12 weeks, or 16 weeks of the administering of inhaled treprostinil.

218. The INCREASE study demonstrated a statistically significant reduction of at least one exacerbation of the interstitial lung disease of PH-ILD patients.

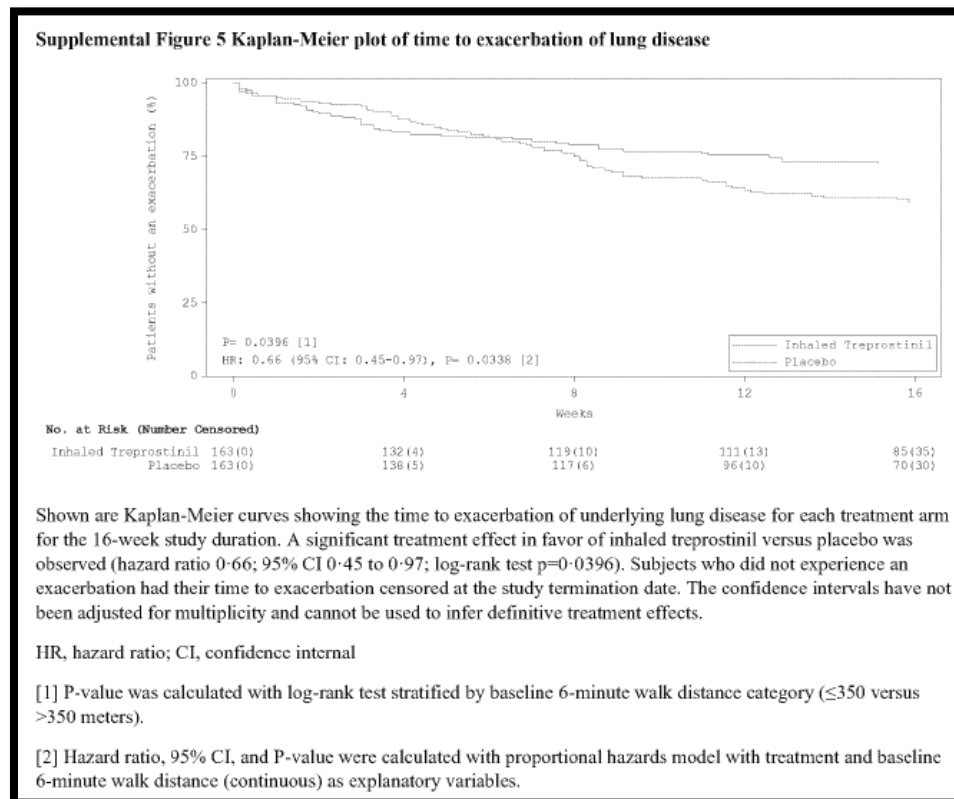
219. Fisher’s exact test is a standard method for assessing the statistical significance of differences between counts of an outcome in one group as compared to counts of the same outcome in a comparison group, where each subject experiences the outcome either once or not at all.

220. The chi-squared test is an alternative to the Fisher’s exact test for assessing the difference between two groups in the fraction of individuals experiencing an event, but when the total number of events observed is small, the p-value calculated using the chi-squared method can be unreliable, so in that case many statistics texts recommend the Fisher test. When the number of events is modest (say more than 10), the results from the two tests are generally in close agreement.

221. Waxman 2021 reported a statistically significant reduction in exacerbations of ILD using a Fisher’s exact test, reporting significantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (43 [26.4%] vs. 63 [38.7%]; P =

0.02 by Fisher's exact test), which is the data reported in the '327 patent.

222. Supplemental Figure 5 of Nathan 2021 depicts a Kaplan-Meier plot of time to exacerbation of lung disease that demonstrates a significant treatment effect in favor of inhaled treprostinil over placebo:



223. The Kaplan-Meier curve (i.e., a survival curve) is a statistical method used to show how the fraction of individuals who have not experienced a particular event varies as a function of time since initiation of treatment—the curve shows the probability over time of surviving without experiencing the event—and the method correctly takes account of all information available from each individual in the case that some individuals have incomplete information.

224. The log-rank test is a statistical method for assessing whether two survival curves differ.

225. The hazard ratio is a measure comparing two survival curves.

226. The National Cancer Institute defines a hazard ratio as: A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.

227. The INCREASE Clinical Study Report reports the reduction in exacerbations in the inhaled treprostinil group was statistically significant using a Chi-squared test ( $p=0.0180$ ), representing a 34% reduction in risk.

228. The INCREASE study demonstrated a statistically significant reduction of clinical worsening events due to the interstitial lung disease of PH-ILD patients. The clinical worsening events comprise at least one hospitalization for cardiopulmonary indication and a decrease in a 6MWD by more than 15% compared to a baseline 6MWD prior to the administering of inhaled treprostinil to the PH-ILD patients.

229. Table 2 and Figure S5 of Waxman 2021 report a statistically significant reduction of clinical worsening events due to ILD using a log-rank test, reporting clinical worsening occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92;  $P = 0.04$  by the log-rank test), which is the same clinical worsening data recited in the Yutrepia™ label:

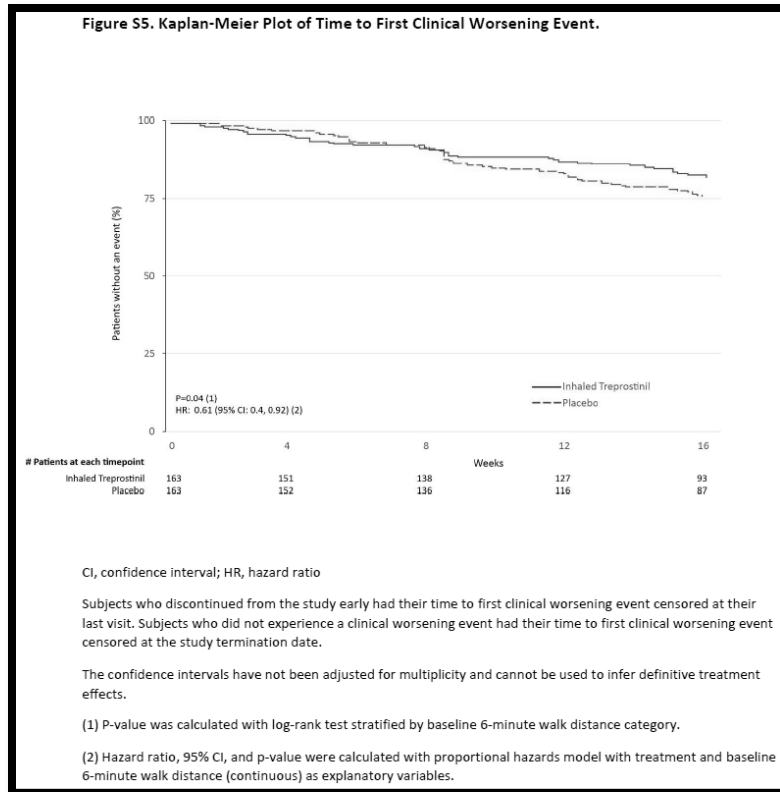
Table 2. Summary of Primary and Secondary End Points.*				
End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		

\* Plus-minus values are means  $\pm$ SE, unless otherwise indicated. For secondary end points, the confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NT-proBNP denotes N-terminal pro-B-type natriuretic peptide.

\*\* This is a hazard ratio, calculated from a Cox proportional-hazards model. The P value was calculated with the use of a log-rank test stratified by the baseline 6-minute walk distance category.

230. Table 2 of Waxman 2021 reports that 31 of 163 patients treated with inhaled treprostinil and 50 of 163 patients treated with placebo experienced at least one of hospitalization for cardiopulmonary indication and a decrease in a 6MWD by more than 15% compared to a baseline 6MWD prior to administration of the study treatment, and this difference is statistically significant ( $p=0.021$ , by Fisher's exact test).

231. Waxman 2021 also reported the data relating to clinical worsening events in a Kaplan-Meier plot, which is the same plot provided in Figure 1 of the '327 patent and Figure 5 of the Yutrepia™ label:



232. The INCREASE study demonstrated a statistically significant improvement of forced vital capacity in PH-ILD patients after 8 weeks, 12 weeks, or 16 weeks of the administering of inhaled treprostinil.

233. Waxman 2021 indicates a statistically significant improvement in % predicted FVC using MMRM analysis after 8 weeks ( $p=0.01$ ) and 16 weeks ( $p=0.03$ ) in Table S6, which is the same data reported in Table 1 of the '327 patent:

Table S6. Analysis of Lung Function Test Parameters Using Mixed Model Repeated Measurement.				
Variable			Contrast: Inhaled treprostinil - Placebo	
Visit			Estimated Difference	
Treatment	N	LS Mean	(95% CI)	P-value
FVC (mL)				
Week 8				
Inhaled treprostinil	142	5.49	28.47	0.35
Placebo	141	-22.98	(-30.81, 87.74)	
Week 16				
Inhaled treprostinil	130	9.77	44.40	0.21
Placebo	126	-34.63	(-25.25, 114.05)	
FVC (% predicted)				
Week 8				
Inhaled treprostinil	142	0.77	1.79	0.01
Placebo	141	-1.02	(0.37, 3.21)	
Week 16				
Inhaled treprostinil	130	1.07	1.80	0.03
Placebo	126	-0.72	(0.20, 3.39)	

234. Nathan 2021 reported a statistically significant improvements in absolute FVC for the IIP subpopulation after 16 weeks (108.2 mL; SE 46.9; 95% CI 15.3 to 201.1;  $p=0.023$ ); for the idiopathic pulmonary fibrosis (IPF) subpopulation after 16 weeks (168.5 mL; SE 64.5; CI 40.1 to 297.0;  $p=0.011$ ); and in % predicted FVC for the IIP and IPF subpopulations after 8 and 16 weeks (IIP subpopulation:  $p$ -value of  $p=0.037$  after 8 weeks and  $p=0.0096$  after 16 weeks; IPF subpopulation:  $p$ -value of  $p=0.038$  after 8 weeks and  $p=0.015$  after 16 weeks). This same data is reported in Examples 1 and 3 of the '327 patent.

235. The INCREASE study demonstrated an improvement in FVC in PH-ILD patients by at least 20 mL after 8 weeks, 12 weeks, or 16 weeks of the administering of inhaled treprostinil.

236. The INCREASE study's findings were not a foregone conclusion.

237. With the INCREASE study completed, the INCREASE findings demonstrate the outcomes that can be expected when patients with PH-ILD are administered inhaled treprostinil for multiple weeks.

238. The INCREASE study, which was carried out according to its study design, means



the INCREASE results typify results from a broad range of clinical settings as well as patient demographics.

239. With the INCREASE study completed, the INCREASE findings also demonstrate that administering Tyvaso<sup>®</sup> to PH-ILD patients in a manner consistent with the dosing regimen used in INCREASE provides one or more of the following statistically significant treatment effects: improved 6MWD, reduced plasma NT-proBNP levels, improved force vital capacity, reduced risk of exacerbations due to the underlying lung disease, and reduced risk of clinical worsening events due to the underlying lung disease.

240. PH-ILD patients administered Tyvaso<sup>®</sup> in a manner consistent with the dosing regimen used in INCREASE would be more likely than not to exhibit one or more of the following treatment effects: improved 6MWD, reduced plasma NT-proBNP levels, improved force vital capacity, reduced risk of exacerbations due to the underlying lung disease, and reduced risk of clinical worsening events due to the underlying lung disease.

### **C. Defendant's Proposed Product**

#### **1. Overview**

241. On January 24, 2020, Defendant submitted Defendant's 505(b)(2) Application under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to FDA seeking approval to manufacture, market, and sell Defendant's Proposed Product.

242. Plaintiff's Tyvaso<sup>®</sup> product was the Reference Listed Drug ("RLD") upon which Defendant's § 505(b)(2) Application was based.

243. On July 24, 2023, Defendant filed an amendment to its 505(b)(2) Application that added the indication "[t]reatment of patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability" to the Proposed Product's label. This language mimicked the PH-ILD indication that Plaintiff had previously

obtained for Tyvaso<sup>®</sup> in 2021.

244. Defendant's Proposed Product will be sold under the tradename Yutrepia<sup>™</sup>.

245. The internal development name for Defendant's Proposed Product was "LIQ861."

246. Yutrepia<sup>™</sup> is a dry powder formulation of treprostinil sodium contained in capsules in 4 strengths: 26.5 mcg, 53 mcg, 79.5 mcg, and 106 mcg.

247. Yutrepia's<sup>™</sup> dry powder formulation will be delivered to patients via inhalation using a supplied capsule-based inhaler.

248. The inhaler supplied with and used to administer Yutrepia<sup>™</sup> is the RS00 Model 8 Monodose dry powder inhaler ("DPI") manufactured by Plastiap S.p.A. ("Plastiap RS00 Inhaler").

249. Defendant stated that it intends to commercialize its Proposed Product for its PH-ILD indication immediately upon receiving final FDA approval.

250. Defendant confirmed that Defendant will market Yutrepia<sup>™</sup> to the same PH-ILD patients for which Tyvaso<sup>®</sup> or Tyvaso DPI<sup>®</sup> are or can be prescribed.

251. Defendant confirmed that Yutrepia<sup>™</sup> does not change how treprostinil acts, and Yutrepia's<sup>™</sup> formulation provides the ability for the treprostinil to act how treprostinil should act.

## **2. Defendant's § 505(b)(2) Application (NDA No. 213005)**

252. Since at least Defendant's May 9, 2016 Pre-IND meeting, Defendant has represented that Yutrepia<sup>™</sup> and Tyvaso<sup>®</sup> have the same active ingredient and same inhaled route of administration, but differences in dosage form (inhalation powder versus liquid aerosol), differences in excipients, and inhalation devices (DPI versus nebulizer) justified the 505(b)(2) pathway.

253. [REDACTED], Defendant has been on notice of FDA's rules regarding the 505(b)(2) pathway—e.g., 21 C.F.R. § 314.54—and FDA's draft guidance regarding the

505(b)(2) pathway and [REDACTED]

[REDACTED].

254. [REDACTED] that the 505(b)(2) pathway requires establishing a bridge between Yutrepia™ and Tyvaso® to demonstrate that Yutrepia's™ reliance on Tyvaso® is scientifically justified, and [REDACTED].

255. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



label and reach alignment with the FDA on the content of the label based on the labeling of the reference listed drug, Tyvaso.” Defendant’s letter to FDA posed several questions, including the following:

**Question 2:** “Does the Division agree that existing clinical efficacy and safety data for treprostinil (described in the Tyvaso PIs and peer-reviewed literature), in addition to data from Liquidia’s completed clinical studies in PAH, are sufficient in scope to file a 505(b)(2) supplemental NDA indicating Yutrepia for the treatment of patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability?”

267. Defendant confirmed that its proposed sNDA for Yutrepia™ consisted of the INCREASE study and supportive data, including three-years of safety data.

268. Both Waxman 2021 and Nathan 2021 had been published in peer-reviewed scientific journals prior to April 8, 2022.

269. On May 25, 2022, FDA responded to Defendant’s April 8 2022 Meeting Request Letter. FDA’s response included the following answer to Defendant’s Question 2:

Your proposed sNDA consists of data from the 16-week randomized, double-blind, placebo controlled, multi-center trial (INCREASE) in patients with PH-ILD and supportive data, including 3 years of safety data, from the PAH program. This is acceptable.

270. FDA’s May 25, 2022 response confirmed that no further clinical trial data were needed to support approval of Yutrepia™ for PH-ILD if Defendant relied on FDA’s previous nonclinical safety findings of Tyvaso® that Defendant relied on in the original NDA 213005 via the § 505(b)(2) pathway and data from UTC’s INCREASE trial. FDA also expressly acknowledged that Defendant was proposing to pursue this PH-ILD indication via the 505(b)(2) pathway and provided Defendant notice and instructions of what that entails.

271. Upon receipt of FDA’s May 25, 2022 response, Dr. Jennifer Weidman, Defendant’s Vice President of Global Regulatory Affairs expressed confidence that Defendant would be able

to expand Yutrepia's™ indication statement to include the PH-ILD without the need to submit additional preclinical or clinical data.

272. At his October 16, 2024 deposition, Defendant's Chief Medical Officer and Rule 30(b)(6) designee Rajeev Saggar, M.D. testified as follows:

**Q.** Okay. But as far as you are concerned, even though you had nothing to do with actually conducting the INCREASE study, you deserved to be able to take advantage of its results?

**A.** Yes, we do. That's correct.

[REDACTED]

274. As of July 24, 2023, Defendant had not conducted or sponsored any clinical trial studying the use of Yutrepia™ in human patients with PH-ILD.

275. On August 16, 2024, the FDA granted Defendant tentative approval to market and sell the Proposed Product in the United States, including for its PH-ILD indication.

276. FDA tentatively approved Yutrepia™ for PH-ILD on a 505(b)(2) application in the absence of any clinical data reflecting Yutrepia™ administration to PH-ILD patients.

277. Defendant has not done any additional studies outside of the studies listed in Defendant's § 505(b)(2) Application except for the ongoing local safety study LTI-302 and the ASCENT study. The ASCENT study began after Defendant amended Yutrepia's™ label to include the PH-ILD indication.

278. Defendant stated that the ASCENT study has no regulatory status in regards to the FDA's consideration of Yutrepia's™ approval, including Yutrepia's™ approval for PH-ILD.

279. Yutrepia's™ tentative approval for a PH-ILD indication relies entirely on

Plaintiff's INCREASE data for safety and efficacy and relies on LTI-102 for the bridge that the § 505(b)(2) pathway requires.

**3. Defendant's Proposed Label**

281. Defendant's Proposed Product will be supplied with a package insert ("Proposed Label"), which provides information regarding that Product and how it should be administered.

282. Defendant's Proposed Label describes Defendant's Proposed Product as being "indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability."

283. Defendant's Proposed Label instructs healthcare providers to "[a]dvice the patient to read the FDA-approved patient labeling (Instructions for Use)" and to "[t]rain patients in the administration process for YUTREPIA, including dosing, inhaler preparation, administration, cleaning, and maintenance, according to the instructions for use [*see Instructions for Use*]."

284. Defendant's Proposed Label identifies the ingredients in Defendant's Proposed Product as: treprostinil sodium (the active ingredient) and inactive ingredients including L-leucine, polysorbate 80, sodium citrate, sodium chloride, and trehalose.

285. Defendant's Proposed Label states that "the dry powder [is] contained in [] HPMC capsule[s]" which have a colored cap and a clear body.

286. Defendant's Proposed Label states every 5mg of Yutrepia™ consists of 28µg of treprostinil sodium salt, which is equivalent to 26.5µg of treprostinil.

287. Defendant's Proposed Label, Instructions for Use, and packing state Yutrepia™ should only be delivered using the capsule-based inhaler.

288. Defendant's Proposed Label describes Defendant's Proposed Product as

“Yutrepia™ (treprostinil) inhalation powder, for oral inhalation” and states that “Yutrepia capsules are for oral inhalation only and should be used only with the supplied inhaler.”

289. Defendant’s Proposed Label describes Defendant’s Proposed Product as being contained in capsules available in four different dosage strengths of treprostinil sodium: 26.5 mcg, 53 mcg, 79.5 mcg, and 106 mcg. Dosage strengths above 106 mcg are achieved by instructing a patient to inhale the contents of more than one capsule in a single administration event.

290. Defendant’s Proposed Label describes administration of Yutrepia™ 3 to 5 times per day in 2 breaths.

291. Defendant’s Proposed Label describes instructions for determining a starting dose of Defendant’s Proposed Product (i) in treprostinil-naïve patients and (ii) in patients transitioning from Tyvaso® (treprostinil inhalation solution) to Defendant’s Proposed Product.

292. Defendant’s Proposed Label describes that “[i]n patients naïve to treprostinil, therapy should begin with 26.5 mcg 3 to 5 times per day, in 2 breaths based on patient response.”

293. Defendant’s Proposed Label provides a table to identify the starting dose of the Proposed Product for patients transitioning from Tyvaso®. The table provides a recommended starting dose equivalent to a patient’s current Tyvaso® dose to be administered “3 to 5 times per day, in 2 breaths.” The table correlates Tyvaso® dosing with Yutrepia™ dosing, and the “3 to 5 times per day, in 2 breaths” correspond to Tyvaso® QID dosing. The table is replicated below:

Current Tyvaso Dose*	YUTREPIA Dose
Breaths	mcg
≤5	26.5
≥6 and ≤8	53
≥9 and ≤11	79.5
≥12 and ≤14	106
≥15 and ≤17	132.5
≥18	159

294. Defendant’s Proposed Label describes dosing treprostinil-naïve patients to begin



with 26.5 mcg of Yutrepia™ 3 to 5 times per day, in 2 breaths. This dosing, when converted to delivered dosage, is nearly identical to the recommended initial dose in the INCREASE study and the initial dosage on the Tyvaso® and Tyvaso DPI® labels.

295. Defendant's Proposed Label describes dosing beyond the initial dose for PH-ILD patients: "In treprostinil-naïve patients and those transitioning from treprostinil inhalation solution, dose increases of 26.5 mcg per dose each week may be implemented, as tolerated."

296. Defendant's Proposed Label instructs that "dose increases of 26.5 mcg per dose each week may be implemented, as tolerated[,]" for all patients and that the "target maintenance dosage is 79.5-106 mcg, 4 times daily," which convert to delivered dosages aligning with the dosing regimen used in the INCREASE study and correspond to dosages on the Tyvaso® and Tyvaso DPI® labels.

297. The Defendant's Proposed Label's conversion tables demonstrate that dosing instructions provided by Yutrepia's™ tentatively approved label's "2 Dosage AND ADMINISTRATION" section of the "FULL PRESCRIBING INFORMATION" and "DOSAGE AND ADMINISTRATION" section of the "HIGHLIGHTS OF PRESCRIBING INFORMATION" align with the dosing regimen of the INCREASE study.

298. The Defendant's Proposed Label's instruction to increase doses by 26.5 µg per dose each week as tolerated, aligns with the rate at which Tyvaso® dosing was titrated upward during the INCREASE study.

299. The Defendant's Proposed Label's target maintenance dosage (79.5 µg to 106 µg) correspond to the INCREASE study's target and maximum doses respectively.

300. The Defendant's Proposed Label's twice instructs administering Yutrepia™ to PH-ILD patients consistent with the INCREASE study.

301. Defendant's Proposed Label and Instructions For Use provide the two-breath-per-capsule instruction to ensure that patients completely inhale a capsule's contents.

302. Defendant's Proposed Label recites absorption and PK data from LTI-102:

**12.3 Pharmacokinetics**

Absorption

in healthy volunteer studies, the systemic exposure (AUC and  $C_{max}$ ) post-inhalation was shown to be proportional to the YUTREPIA doses administered (25 mcg – 150 mcg). The treprostinil mean  $C_{max}$ , mean AUC<sub>inf</sub> and median  $T_{max}$  following a single inhaled target maintenance dose of 79.5 mcg YUTREPIA were 1.48 ng/mL, 1.04 hr.ng/mL and 0.13 hr, respectively.

303. Defendant's Proposed Label recites half-life data from LTI-102:

Elimination

Following inhaled administration of YUTREPIA, disposition and elimination is monophasic with a half-life of approximately 30 minutes.

304. Defendant's Proposed Label describes the clinical studies Defendant uses to support each of its indications.

305. Defendant's Proposed Label identifies only the INCREASE study in its clinical studies section supporting the PH-ILD indication for Defendant's Proposed Product.

306. Defendant's Proposed Label states that the UTC-sponsored INCREASE study "was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD."

307. Defendant's Proposed Label describes certain INCREASE study results.

308. Defendant amended Yutrepia's™ proposed label July 24, 2023 adding the PH-ILD indication under the "INDICATIONS AND USAGE" section of the "HIGHLIGHTS OF PRESCRIBING INFORMATION" page that directs to the indication under "1. INDICATIONS AND USAGE" of the "FULL PRESCRIBING INFORMATION," and adding under "14 CLINICAL STUDIES": "14.2 Pulmonary Hypertension Associated with ILD (WHO Group 3),"

which imports the corresponding description of the INCREASE study from the Tyvaso<sup>®</sup> labels.

309. Defendant admits that Yutrepia's<sup>™</sup> proposed label copies the same language described in the PH-ILD indication from the Tyvaso<sup>®</sup> label and relies on the key results of the INCREASE study.

310. Defendant's Proposed Label copies the PH-ILD indication of the Tyvaso<sup>®</sup> Label nearly verbatim, provides the same instructions for use in particular populations, contains the same warnings, and relies on the same clinical data from INCREASE to support its PH-ILD indication.

311. Defendant's Proposed Label's PH-ILD indications recite disease etiology breakdowns that are consistent with the subpopulations in the INCREASE study.

312. Defendant's Proposed Label's PH-ILD indications directly or indirectly refer to "14 CLINICAL STUDIES": "14.2 Pulmonary Hypertension Associated with ILD (WHO Group 3).".

313. Defendant's Proposed Label copies a number of sections, nearly verbatim, from the Tyvaso<sup>®</sup> Label including, but not limited to, the clinical studies section.

314. Defendant's Proposed Label copies, nearly verbatim, the clinical studies section of the Tyvaso<sup>®</sup> Label with respect to the "Pulmonary Arterial Hypertension" and "Pulmonary Hypertension Associated with ILD" subsections.

315. Defendant's Proposed Label copies, nearly verbatim, the Tyvaso<sup>®</sup> Label's discussion of the INCREASE study within its clinical studies section, including the same selection of data from INCREASE.

316. Defendant's Proposed Label identifies certain doses of Yutrepia<sup>™</sup> as being "equivalent" to corresponding doses of Tyvaso<sup>®</sup>, including in the specific context of the INCREASE trial:

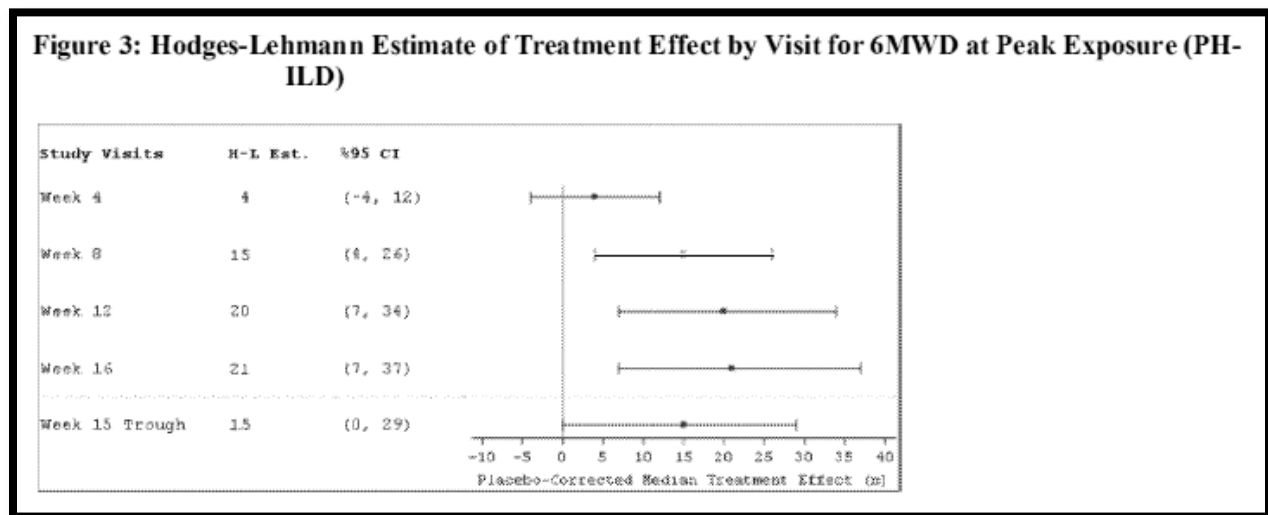
#### 14.2 Pulmonary Hypertension Associated with ILD (WHO Group 3)

INCREASE was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD. Enrolled study patients predominately had etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%). The mean baseline 6MWD was 260 meters.

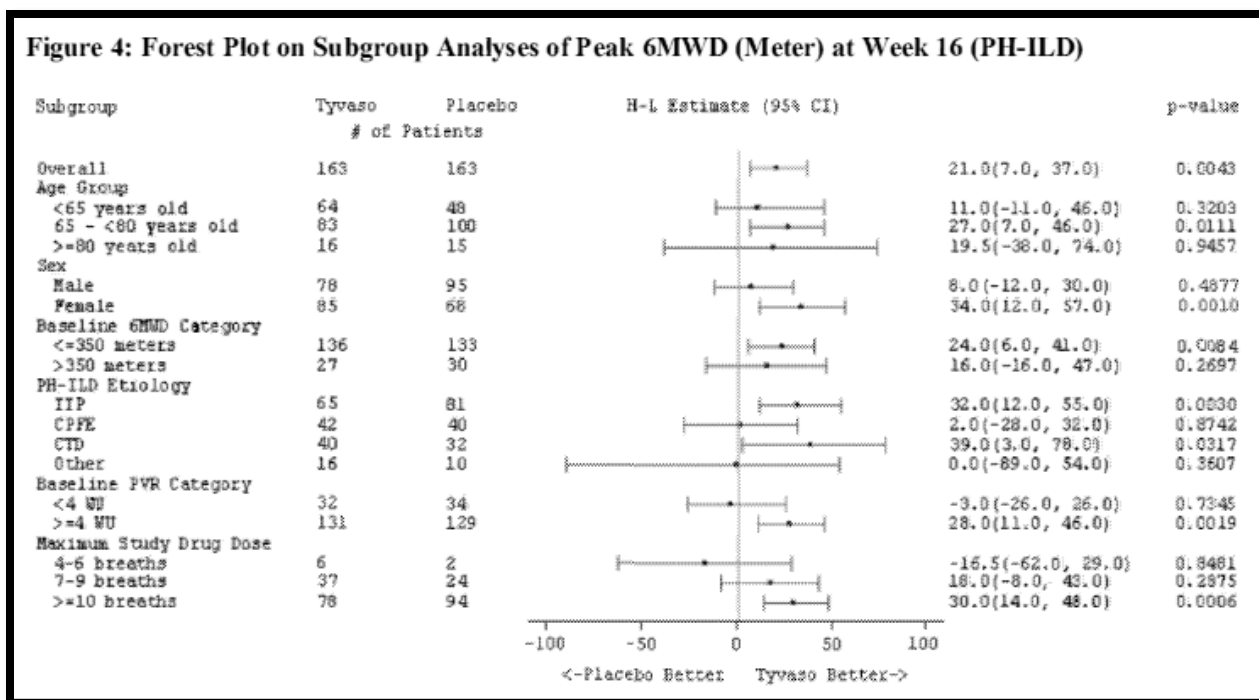
Patients in the INCREASE study were randomized (1:1) to either placebo or treprostinil inhalation solution in four daily treatment sessions with a target dose of 9 breaths (equivalent to 79.5 mcg YUTREPIA) per session and a maximum dose of 12 breaths (equivalent to 106 mcg YUTREPIA) per session over the course of the 16-week study. Approximately 75% of patients randomized to treprostinil inhalation solution titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of patients randomized to treprostinil inhalation solution reaching a dose of 12 breaths, 4 times daily during the study. The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16. Patients receiving treprostinil inhalation solution had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 ( $p=0.004$ ) using HodgesLehmann estimate (Figure 3).

317. Defendant's Proposed Label makes clear that Defendant is seeking approval for the same PH-ILD indication as Tyvaso<sup>®</sup> based on the same INCREASE results.

318. Defendant's proposed label provides the INCREASE study's placebo-corrected median 6MWD treatment effect results using Hodges Lehmann estimate with 95% confidence intervals, and failure of confidence intervals to cross zero indicates statistical significance with the 16 week p-value (0.004) provided:



319. Defendant's Proposed Label reports 16 week analysis of select subgroups using Hodges Lehmann estimate with 95% confidence intervals, and failure of confidence intervals to cross zero indicates statistical significance with p-values also provided:



320. Defendant's Proposed Label includes data from the INCREASE study reporting a statistically significant increase in 6-minute walk distance among PH-ILD patients at week 16 of inhaled treprostinil administration.

321. Defendant's Proposed Label reports an increase by at least 10 m in a PH-ILD patient's 6MWD after 8 weeks, 12 weeks, or 16 weeks of the administering of inhaled treprostinil.

322. Defendant's Proposed Label reports an increase by at least 10 m in a PH-ILD patient's 6MWD after 8 weeks of the administering of inhaled treprostinil.

323. Defendant's Proposed Label reports an increase by at least 15 m in a PH-ILD patient's 6MWD after 12 weeks of the administering of inhaled treprostinil.

324. Defendant's Proposed Label reports an increase by at least 15 m in a PH-ILD patient's 6MWD after 16 weeks of the administering of inhaled treprostinil.

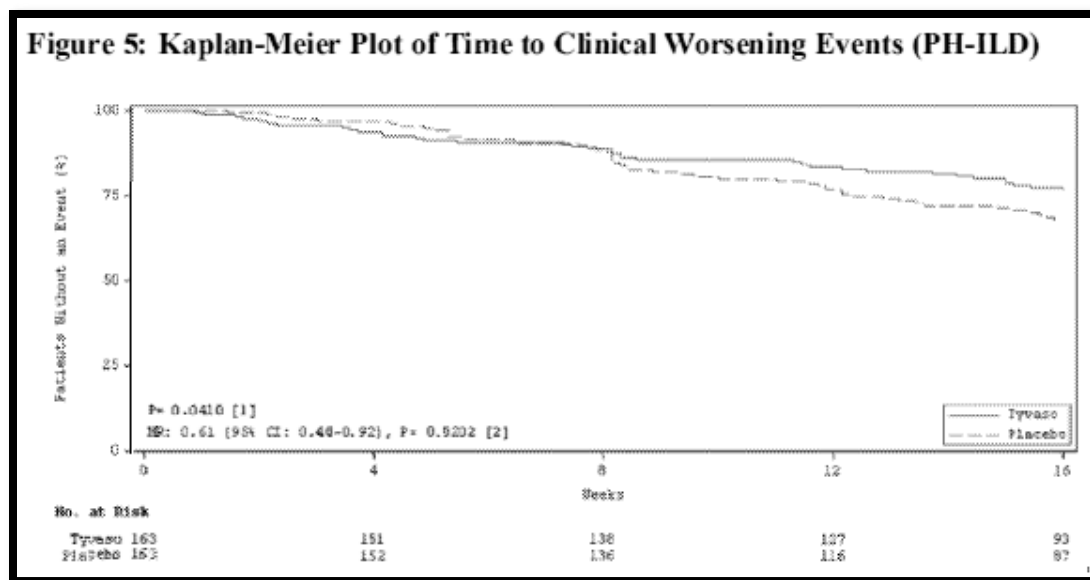
325. Defendant's Proposed Label reports that "[t]ime to clinical worsening in the INCREASE study was defined as the time of randomization until 1 of the following criteria were met: hospitalization due to cardiopulmonary indication, decrease in 6MWD >15% from baseline

directly related to PH-ILD at 2 consecutive visits and at least 24 hours apart, death (all causes), or lung transplantation.”

326. Defendant’s Proposed Label includes data from the INCREASE study reporting a statistically significant increase in the time to first clinical worsening event.

327. Defendant’s Proposed Label states that “[t]reatment with treprostinil inhalation solution in patients with PH-ILD resulted in numerically fewer hospitalizations.”

328. Defendant’s Proposed Label reports a Kaplan-Meier Plot of Time to clinical worsening events along with a log-rank test analysis of time to first clinical worsening event ( $p=0.041$ ) and reports “a 39% overall reduction in the risk of a clinical worsening event ( $HR=0.61$  [95% CI: 0.40, 0.92]” and includes a figure that describes this reduction as statistically significant.



329. Defendant’s Proposed Label provides additional INCREASE study data regarding the frequency of clinical worsening events:

**Table 3: Clinical Worsening Events (PH-ILD)**

		Tyvaso n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
<b>Clinical worsening</b>		37 (22.7%)	54 (33.1%)	0.61 (0.40, 0.92)
<b>First contributing event</b>	<b>Hospitalization due to a cardiopulmonary indication</b>	18 (11.0%)	24 (14.7%)	
	<b>Decrease in 6MWD &gt;15% from baseline directly related to PH-ILD</b>	13 (8.0%)	26 (16.0%)	
	<b>Death (all causes)</b>	4 (2.5%)	4 (2.5%)	
	<b>Lung transplantation</b>	2 (1.2%)	0	

		Tyvaso n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
<b>First of each event</b>	<b>Hospitalization due to a cardiopulmonary indication</b>	21 (12.9)	30 (18.4%)	
	<b>Decrease in 6MWD &gt;15% from baseline directly related to PH-ILD</b>	16 (9.8%)	31 (19.0%)	
	<b>Death (all causes)</b>	8 (4.9%)	10 (6.1%)	
	<b>Lung transplantation</b>	2 (1.2%)	1 (0.6%)	

330. Defendant’s Proposed Label instructs healthcare providers to “[a]dvise the patient to read the FDA-approved patient labeling (Instructions for Use)” and to “[t]rain patients in the administration process for YUTREPIA, including dosing, inhaler preparation, administration, cleaning, and maintenance, according to the instructions for use *[see Instructions for Use]*.”

331. Defendant intends to commercialize its Proposed Product for its PH-ILD indication immediately upon receiving final FDA approval.

#### **4. The LTI-102 Study**

332. LTI-102 was a clinical trial sponsored by Defendant that evaluated the bioavailability and safety of Yutrepia™ relative to Tyvaso® using healthy subjects.

333. The results of the LTI-102 study were published in Roscigno R, et. al., *Comparative bioavailability of inhaled treprostinil administered as LIQ861 and Tyvaso® in healthy subjects*,

VASCULAR PHARM. 138:106840 (2021) (“Roscigno 2021”).

334. Roscigno 2021 states that doses for dry powder formulations—like Yutrepia™—are provided in terms of capsule strength, which refers to the amount of active ingredient within a capsule (“total capsule fill”), not the output available when inhaled (“target delivered dose”), and the target delivered dose is less than the total capsule fill.

335. Roscigno 2021 states nebulized solutions are dosed based on the target delivered dose.

336. Roscigno 2021 states that Yutrepia’s™ 79.5 µg capsule strength achieves a 58.1 µg target dose that corresponds to the 54 µg delivered dose achieved with 9 breaths of Tyvaso® (which was Tyvaso’s® maintenance dose when LTI-102 was conducted). Roscigno 2021 states a 79.5 µg capsule strength was chosen because it has a similar target delivered dose (58.1 µg) as the 54 µg Tyvaso® dose.

337. Roscigno 2021 states that the primary objective of LTI-102 was to assess the comparative bioavailability of these respective doses of Yutrepia™ and Tyvaso®.

338. Roscigno 2021 reports that LTI-102 was a single-center, randomized, open-label, replicate, and crossover study in healthy adults; subjects were randomized 4:1:1 to the “Replicate Group, Comparative Bioavailability Group 1, and Comparative Bioavailability Group 2,” respectively; subjects in the Replicate Group received two Yutrepia™ treatments; subjects in Comparative Bioavailability Group 1 and Comparative Bioavailability Group 2 received a Yutrepia™ dose and a Tyvaso® dose with the order inversed between the two groups; doses were provided on consecutive days, with data collected before dosing and throughout the 6 hours following dosing; subjects remained at the clinical site overnight; samples were collected before dosing and at 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, and 360 minutes after the dose; and some



variability was permitted:  $\pm 1$  minute for the 5, 10, 15, and 20-minute timepoints;  $\pm 5$  minutes for the 30, 45, and 60-minute timepoints; and  $\pm 10$  minutes for the remainder.

339. Roscigno 2021 reports that LTI-102 enrolled healthy male and female subjects between 18 and 45 years of age (inclusive), with a body mass index (BMI) of 18 to 32 kg/m<sup>2</sup>, who abstained from tobacco and nicotine use for at least 2 months prior to screening; subjects were instructed not to take any prescription medication for 14 days or any dietary supplements or over-the-counter drugs for at least 3 days prior to CRU admission through completion of the study; the study excluded those who: had a history of asthma or other respiratory condition; a history of illicit drug or alcohol abuse or positive urine drug screen; were positive for human immunodeficiency virus, hepatitis B, and/or hepatitis C; were pregnant or lactating females; had clinically significant medical or psychiatric history that, in the Investigator's judgment, would compromise the subject's safety or the collection of data; had donated plasma or blood within 7 or 30 days prior to the clinical site admission, respectively; had participated in another investigational drug study within 30 days prior to the clinical site admission; or had surgery within 6 months prior to screening.

340. Roscigno 2021 reports that 24 subjects enrolled in LTI-102, and 23 subjects completed the study, with one subject in the Replicate Group discontinuing after receiving their first Yutrepia<sup>TM</sup> treatments.

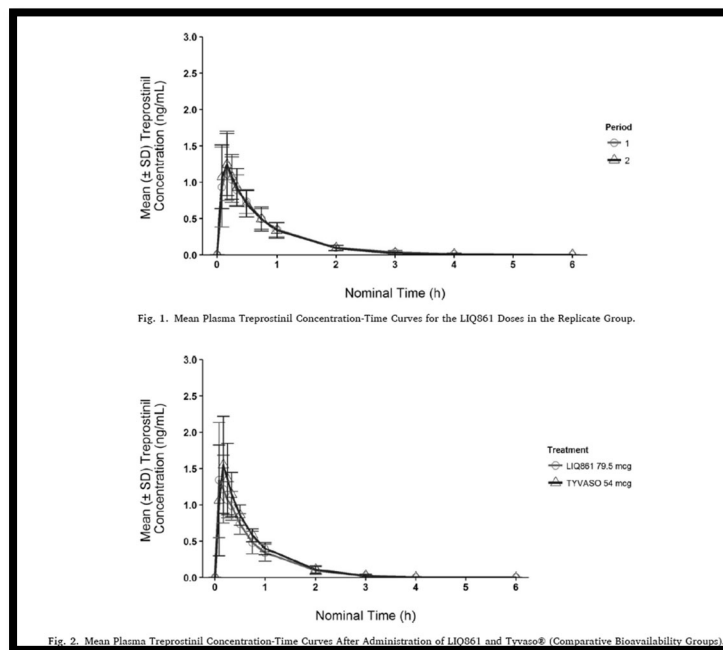
341. Roscigno 2021 reports the following PK data:

**Table 1**  
Treprostinil PK Parameters in Study LTI-102 (Replicate Group and Comparative Bioavailability Group).

Treatment	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>last</sub> (h*ng/mL)	AUC <sub>inf</sub> (h*ng/mL)	t <sub>1/2</sub> (h)
<b>Replicate Group</b>					
LIQ861 Dose 1 (n = 16)	1.25 (0.505)	0.17 (0.10, 0.57)	0.975 (0.198)	1.01 (0.198)	0.647 (0.142)
LIQ861 Dose 2 (n = 15)	1.28 (0.378)	0.17 (0.08, 0.50)	0.950 (0.216)	0.995 (0.209)	0.610 (0.164)
<b>Comparative Bioavailability Groups</b>					
LIQ861 (n = 8)	1.48 (0.668)	0.13 (0.08, 0.33)	1.01 (0.0926)	1.04 (0.102)	0.546 (0.117)
Tyvaso® (n = 8)	1.60 (0.722)	0.17 (0.13, 0.25)	1.09 (0.217)	1.14 (0.198)	0.520 (0.0925)

AUC<sub>inf</sub> = area under the plasma concentration versus time curve from time 0 extrapolated to infinite time;  
AUC<sub>last</sub> = AUC from time 0 to time of the last measurable non-zero plasma concentration; C<sub>max</sub> = maximum observed plasma concentration; PK = pharmacokinetic; SD = standard deviation; t<sub>1/2</sub> = half-life; T<sub>max</sub> = time to C<sub>max</sub>.  
Data are from the 16 subjects in the Replicate Group who took single doses of LIQ861 on 2 occasions (except for one subject who did not take the second dose) and the 8 subjects in the Comparative Bioavailability Groups who took one dose of LIQ861 and one dose of Tyvaso®. There were 4 subjects in each of the 2 Comparative Bioavailability Groups who took the 2 treatments in the opposite order.  
Data are mean (SD) for all parameters except for T<sub>max</sub> which is median (minimum, maximum).

342. Roscigno 2021 reports the following plasma treprostinil concentration curves:



343. Roscigno 2021 processed the pharmacokinetic data from Comparative Bioavailability Groups according to the standard statistical approach for calculating bioequivalence—average bioequivalence:

Table 2 Comparative Bioavailability Results.		
Treprostnil PK Parameter	LS GMR	
	Point Estimate	90% CI
$AUC_{inf}$	0.923	(0.802, 1.064)
$AUC_{last}$	0.947	(0.812, 1.103)
$C_{max}$	0.931	(0.819, 1.059)

$AUC_{inf}$  = area under the plasma concentration versus time curve from time 0 extrapolated to infinite time;  
 $AUC_{last}$  = AUC from time 0 to time of the last measurable non-zero plasma concentration; CI = confidence interval;  $C_{max}$  = maximum observed plasma concentration; LS GMR = Least Squares Geometric Mean Ratio LIQ861 (79.5 µg): Tyvaso® (54 µg); PK = pharmacokinetic.  
 Data are from the 8 subjects in the Comparative Bioavailability Groups.

344. Roscigno 2021 reports that the 90% confidential intervals were entirely within the 80%-125% range, implicitly acknowledging that Yutrepia™ and Tyvaso® are bioequivalent, and concludes that Yutrepia™ and Tyvaso® exposure and bioavailability were comparable.

345. Roscigno 2021 states the target delivered dose is a more valid comparison of the doses than the labeled dose strength because of the different labeling conventions for the 2 types of drug delivery systems, and thus the respective doses of Yutrepia™ (79.5 µg capsule strength; 58.1 µg target delivered dose) and Tyvaso® (9 breaths, i.e., a 54 µg) doses were expected to result in approximately the same treprostnil exposure.

346. Roscigno 2021 states that Defendant's LTI-101—a randomized, double-blind, placebo-controlled, single ascending dose study—established the dose proportionality of treprostnil exposure and its tolerability after administration of Yutrepia™ in the 25 to 150 µg dose range.

347. Roscigno 2021 states that the LTI-101 pharmacokinetic data was similar to the published treprostnil PK profile after Tyvaso® administration and LTI-102 was only conducted to examine the pharmacokinetics of Yutrepia™ and Tyvaso® in the same study.

348. Roscigno 2021 states that LTI-102 was conducted to establish a PK bridge between treprostnil administered as LIQ861 (capsule strength of 79.5 µg and delivered via DPI with target

delivered dose of 58.1 µg) and the reference drug, treprostinil solution for inhalation (Tyvaso®) (labeled strength with 9 breaths for a target delivered dose via nebulizer of 54 µg).

349. Roscigno 2021 states that “The comparative bioavailability assessment demonstrated that treprostinil exposure from a single capsule dose of 79.5 µg LIQ861 (approximate delivered dose 58.1 µg) is comparable to treprostinil exposure from 9 beaths of Tyvaso® (approximate delivered dose 54 µg).”

350. Roscigno 2021 states that “comparable treprostinil bioavailability was demonstrated after administration of LIQ861 [(Defendant’s Proposed Product)] (79.5 µg capsule) and Tyvaso® (9 breaths for a 54-mcg dose), and that both were well tolerated.”

351. Consistent with Roscigno 2021, Defendant’s regulatory filings state that “[t]he established comparable bioavailability of LIQ861 to Tyvaso facilitates a simple transition for patients to LIQ861 from Tyvaso and provides physicians with a titration methodology similar to the well-known approach for Tyvaso.”

352. Defendant represents that its Proposed Product has “[c]omparable pharmacokinetics to Tyvaso®.”

353. After completion of LTI-101 and LTI-102, converting between Yutrepia™ and Tyvaso® dosing was routine and formulaic.

354. Roscigno 2021 employed standard statistical methods for analyzing the pharmacokinetic data and for assessing relative bioavailability: an MMRM model applied to log-transformed individual pharmacokinetic parameters.

355. Bioavailability studies are typically single-center, single-arm studies but do not suffer from the associated drawbacks because they recruit healthy individuals, they employ cross-over designs, and the order in which a subject receives the treatments is randomized.

## **5. The INSPIRE Study (LTI-301)**

356. The INSPIRE study, which Defendant also refers to as “LTI-301,” was a Phase 3 clinical trial sponsored by Defendant that studied the safety and tolerability of Defendant’s Proposed Product in PAH patients over the course of 1 year.

357. The INSPIRE study included both treprostinil-naïve patients as well as patients who were previously taking Tyvaso<sup>®</sup> nebulized solution before transitioning to Yutrepia<sup>™</sup>.

358. Defendant’s Proposed Label refers and cites to the INSPIRE study.

359. The results of the INSPIRE study were reported in Hill, N., et al., *INSPIRE: Safety and tolerability of inhaled Yutrepia (treprostinil) in pulmonary arterial hypertension (PAH)*, PULM. CIRC. 12(3):e12119 (2022) (“Hill 2022”).

360. Hill 2022 states that “The present Phase 3 trial (Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil [INSPIRE], LTI-301) was performed in consultation with the Federal Drug Administration to evaluate the safety and tolerability of Yutrepia in PAH patients who were transitioned from a stable dose of nebulized treprostinil or were receiving no more than two approved background oral PAH therapies.”

361. Hill 2022 states that “transition patients initiated Yutrepia at a dose comparable to their nebulized treprostinil dose.”

362. Hill 2022 states that “Patients receiving stable doses of nebulized treprostinil successfully transitioned to Yutrepia with no significant safety concerns.”

## **6. Defendant’s Marketing Materials for Yutrepia<sup>™</sup>**

363. Defendant has made preparations to commercially market Defendant’s Proposed Product for PH-ILD.

364. Defendant’s Proposed Product targets the same set of PH-ILD patients as Tyvaso<sup>®</sup> and Tyvaso DPI<sup>®</sup> and is intended to compete in the same market.

365. Defendant amended Defendant's § 505(b)(2) Application to pursue alignment with the Tyvaso<sup>®</sup> labeling and expand the indication statement for Defendant's Proposed Product to include Tyvaso's<sup>®</sup> PH-ILD indication.

366. Defendant has prepared various marketing materials to support its intended commercial launch of Yutrepia<sup>™</sup>.

367. Defendant's marketing materials for Defendant's Proposed Product will be distributed to healthcare providers, patients, and/or payors.

368. Defendant has prepared a Yutrepia<sup>™</sup> "Formulary Kit" for distribution to payors. The Formulary Kit relies on the INCREASE study when discussing Yutrepia's<sup>™</sup> approved status for PH-ILD indication, with an acknowledgement that the INCREASE study demonstrated that administering treprostinil in PH-ILD patients improves 6MWD, reduces plasma NT-proBNP levels, and lowers clinical worsening risk.

369. Defendant has prepared a Yutrepia<sup>™</sup> Approved Product Dossier for distribution to payors. The Approved Product Dossier clearly links Yutrepia's<sup>™</sup> approval for Tyvaso's<sup>®</sup> PH-ILD indication to the INCREASE study and highlights that the INCREASE study demonstrated that treprostinil administration in PH-ILD patients resulted in improved 6MWD, reduced plasma NT-proBNP levels, and reduced risk of clinical worsening.

370. Defendant has prepared marketing materials, including slide presentations, that are directed for distribution to healthcare providers. These materials features the INCREASE study's 6MWD, NT-proBNP, and clinical worsening data as representative of the clinical performance of Yutrepia<sup>™</sup> in PH-ILD patients.

371. Defendant has prepared marketing materials, including a product brochure, that are directed for distribution to PH-ILD patients. These materials reference the INCREASE study's

6MWD and clinical worsening findings in advertising how Yutrepia™ may help those with PH-ILD.

372. Defendant's marketing materials expressly describe INCREASE study data, including data found in Defendant's Proposed Label and in peer-reviewed literature.

373. Defendant's marketing materials rely on Plaintiff's INCREASE data as a proxy for how Defendant's Proposed Product will perform in PH-ILD patients.

374. Defendant's marketing materials demonstrate Defendant's intent and expectation that its Proposed Product be administered to PH-ILD patients in accordance with Defendant's Proposed Label.

375. Defendant's marketing materials demonstrate Defendant's intent and expectation that patients receiving Defendant's Proposed Product will more likely than not achieve the same benefits and results observed in the INCREASE study.

**D. The INCREASE Study's Results are Attributable to Yutrepia™**

376. As described and represented to the FDA in Liquidia's § 505(b)(2) Application, including the proposed label, administration of Yutrepia™ consistent with Defendant's Proposed Label or in a clinical study conducted similar in design and conduct as the INCREASE study would more likely than not produce results comparable to those generated by the INCREASE study.

377. It is more likely than not that Yutrepia™ will demonstrate the same treatment effects as those demonstrated by the INCREASE study, including in the same or similar magnitudes as those demonstrated by the INCREASE study when Yutrepia™ is administered according to Defendant's Proposed Label.

378. If a healthcare provider administers Yutrepia™ to PH-ILD patients in an amount consistent with the amounts delivered in the INCREASE study, that administration would more likely than not produce efficacy results consistent with the INCREASE study in view of

Yutrepia™ and Tyvaso's® comparable bioavailability.

379. The INCREASE study's findings inform the efficacy and safety of other inhaled products with treprostinil as their only active ingredient—if such a product administers treprostinil to PH-ILD patients in an amount consistent with the amounts delivered in the INCREASE study, and if administering that product provides comparable bioavailability—that product would be expected to produce efficacy results consistent with the INCREASE study, provided that the product did not introduce additional safety or tolerability issues not present with Tyvaso®.

380. The principle behind FDA permitting product sponsors to rely on FDA's clinical efficacy and safety findings of the sponsor-selected RLD if the product sponsors establish the requisite biocomparability or bioequivalence of their product with respect to the RLD is the expectation that the quality of the RLD's clinical efficacy and safety findings provides confidence in their reproducibility.

381. Inhaled products comprising treprostinil as their only active ingredient and that exhibit comparable bioavailability, safety, and tolerability to Tyvaso®, and that are administered consistent with the INCREASE study dosing regimen, would be expected to replicate the INCREASE study's prespecified efficacy and safety endpoints, including endpoints that were examined after unblinding but not prespecified in the study protocol would be more likely than not to be replicated—and this would be true whether or not a particular endpoint was included among those listed on those products' labels.

382. Defendant is seeking FDA approval of its Proposed Product for PH-ILD based solely on Plaintiff's Tyvaso® data in INCREASE.

383. Defendant acknowledges that Yutrepia's™ approval for PH-ILD relies on the INCREASE study and that Yutrepia™ should also be granted the same label as Tyvaso®.



384. A healthcare provider would understand from Defendant's Proposed Label that the approval of Yutrepia for PH-ILD was based on the INCREASE study.

385. Defendant's regulatory communications with FDA expressly state that Defendant will rely on "existing clinical efficacy and safety data for treprostinil (described in the Tyvaso<sup>®</sup> PIs and peer-reviewed literature)" to demonstrate that Yutrepia<sup>™</sup> will be safe and efficacious in PH-ILD patients. The "peer-reviewed literature" referenced in this statement includes publications discussing INCREASE, including Waxman 2021 and Nathan 2021.

386. Defendant has represented to FDA that clinical testing of Defendant's Proposed Product is not required because Defendant's Proposed Product will have comparable efficacy and safety as compared to Tyvaso<sup>®</sup> in PH-ILD patients, e.g., as demonstrated by the results of the INCREASE study.

387. Defendant's approval strategy for the PH-ILD indication for Defendant's Proposed Product depends on Defendant's Proposed Product and Tyvaso<sup>®</sup> performing equivalently in PH-ILD.

388. FDA accepted Defendant's reliance on the INCREASE results in order to support the PH-ILD indication for Defendant's Proposed Product.

389. As a result of Defendant's representations to FDA regarding the expected safety and efficacy of Yutrepia<sup>™</sup> in PH-ILD, FDA did not require Defendant to conduct its own Phase II, III, and/or post-marketing studies to prove that Defendant's Proposed Product was actually safe and effective in improving exercise capacity in PH-ILD patients.

390. Both Defendant and the FDA agree that the INCREASE data is reliable, predictive, and powered enough to reflect the real-world performance of Defendant's Proposed Product for regulatory approval.

391. Defendant has not submitted any of its own clinical data to the FDA to demonstrate that its Proposed Product improves exercise capacity in PH-ILD patients.

392. Defendant has not completed any clinical trials to study the safety and/or efficacy of its Proposed Product in PH-ILD patients.

393. As discussed above, the portions of Defendant's Proposed Label relating to PH-ILD and INCREASE are copied almost verbatim from Plaintiff's package insert for Tyvaso®.

394. The absence of any particular INCREASE data from Defendant's Proposed Label reflects Defendant's intent to copy the Tyvaso® label, not to carve out specific INCREASE results.

395. As discussed above, Defendant's Proposed Label identifies certain doses of Yutrepia™ as being "equivalent" to corresponding doses of Tyvaso®, including in the specific context of the INCREASE trial.

396. As discussed above, Defendant's Proposed Label contains a chart that healthcare providers can use to interconvert between equivalent doses of Yutrepia™ and nebulized Tyvaso®.

397. At his October 16, 2024 deposition, Defendant's Chief Medical Officer and Rule 30(b)(6) designee Rajeev Saggur, M.D. testified as follows:

**Q.** So if there is a way to do -- to give Yutrepia to the same type of PH-ILD patients as were administered Tyvaso in INCREASE, do you think -- does Liquidia believe that Yutrepia's performance would meet or exceed the performance of Tyvaso in the INCREASE study?

**A.** Yes. If the settings were exactly the same, yes, I do believe that.

398. On May 20, 2023 Defendant held a meeting of its "PH-ILD Advisory Board" to discuss its plans to develop Yutrepia™ for PH-ILD. Liquidia CMO Rajeev Saggur invited an outside subject matter expert—Dr. Franck Rahaghi from the Cleveland Clinic—to present on the design, patient demographics, and results of the INCREASE trial. Dr. Saggur invited Dr. Rahaghi to give this presentation because it was "relevant to [Defendant's] interests." Dr. Rahaghi noted as

part of his presentation that “that “because Liquidia was ‘going to inherit the indication [for PH-ILD granted to inhaled Tyvaso in the basis of INCREASE], they’re going to inherit the INCREASE study.”

399. Defendant’s regulatory filings state that “[t]he established comparable bioavailability of LIQ861 to Tyvaso facilitates a simple transition for patients to LIQ861 from Tyvaso and provides healthcare providers with a titration methodology similar to the well-known approach for Tyvaso.”

400. Defendant’s regulatory filings describe comparable bioavailability between Defendant’s Proposed Product and nebulized Tyvaso®: “The comparative bioavailability of LIQ861 and Tyvaso was established in Part 3 of the LTI-102 study, demonstrating that treprostinil exposure from a 79.5 mcg LIQ861 capsule with a targeted delivered dose of approximately 56.6 mcg treprostinil is comparable to that of 9 breaths of Tyvaso (54 mcg dose).”

401. Defendant represents that its Proposed Product has “[c]omparable pharmacokinetics to Tyvaso®.”

402. Defendant relies on comparative PK data between Defendant’s Proposed Product and nebulized Tyvaso® to establish that the two formulations would deliver the same amount of the same active ingredient to PH-ILD patients.

403. As discussed above, Defendant’s marketing materials present INCREASE results to demonstrate how Defendant’s Proposed Product will perform in PH-ILD patients.

404. As discussed above, Defendant represents in its marketing materials its Proposed Product, when used according to its Proposed Label, will perform comparably to how nebulized Tyvaso® performed in INCREASE.

405. Defendant’s Proposed Product will be administered to a single PH-ILD patient with

the intent to create a statistically significant result in view of the INCREASE patient population. The INCREASE patient population is the same patient population on which Defendant's Proposed Product's approval is based.

**E. Defendant's Knowledge of the '327 Patent**

406. Defendant has had knowledge of the '061 application from which the '327 patent issued at least as early as June 29, 2023, the day after the '061 application was issued its notice of allowance. Defendant similarly had knowledge of the allowed claims of the '061 application as of this date.

407. Defendant was closely monitoring the '061 application during its prosecution by Plaintiff at the USPTO.

408. On June 29, 2023, Defendant's Chief Financial Officer Michael Kaseta filed a Form 8-K with the SEC to report that the United States Patent and Trademark Office had issued a notice of allowance for the (then-pending) '061 application on the previous day, June 28, 2023. In this document, Defendant characterized the allowed claims as "generally cover[ing] the treatment of patients having pulmonary hypertension associated with interstitial lung disease ('PH-ILD') through the inhaled administration of treprostinil."

409. On July 3, 2023, Defendant received a news report from "CVrg Sentinel™: Pulmonary Hypertension," which noted the '061 application's notice of allowance, describing it as "potentially a large setback for Liquidia ...." Defendant also received the Q2 2023 CVrg Market Strategies™: Pulmonary Hypertension report on July 11, 2023,<sup>405</sup> which described the '061 application as one of Yutrepia's™ "Weaknesses/Threats."

410. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

411. On July 24, 2023, despite knowledge of the '061 application and the subject matter covered by its allowed claims, Liquidia formally amended Defendants § 505(b)(2) Application to include a PH-ILD indication.

412. [REDACTED]

[REDACTED]

[REDACTED]

413. Defendant's decision to move forward with a PH-ILD indication for Yutrepia™ despite knowledge of the '061 application and '327 patent is further demonstrated by the June 30, 2023 and September 30, 2023 Form 10-Q's that Defendant filed with the SEC, which repeatedly acknowledge that the July 24, 2023 amendment may result in Defendant bringing a new patent infringement suit, and specifically identify any patent issuing from the '061 application.

414. Defendant has had knowledge of the issued '327 patent at least as early as November 30, 2023, when Plaintiff amended its complaint in this matter to assert the '327 patent.

415. Defendant sought approval to market its Proposed Product for PH-ILD with full knowledge of the '327 patent and the '061 application from which it issued.

416. Despite its knowledge of the '327 patent and the '061 application, Defendant continues to push forward with its plans to begin marketing its Proposed Product as soon as it receives final approval.

**F. The ASCENT Study**

417. Defendant is currently performing a clinical trial of Defendant's Proposed Product in PH-ILD patients entitled "An Open-Label Prospective Multicenter Study to Evaluate Safety and

Tolerability of Dry Powder Inhaled Treprostinil in Pulmonary Hypertension” (the “ASCENT study”).

418. The ASCENT study is an open-label, uncontrolled study in which PH-ILD patients are administered Defendant’s Proposed Product in the same manner as described in Defendant’s Proposed Label.

419. Defendant initiated the ASCENT study on December 28, 2023, several months after Defendant had already applied to add a PH-ILD indication for Defendant’s Proposed Product.

420. Defendant initiated the ASCENT study with full knowledge of the ’327 patent as well as Plaintiff’s infringement allegations concerning the ’327 patent in this lawsuit. The ’327 patent was published on October 28, 2021 and issued on November 28, 2023. Plaintiff asserted the ’327 patent against Defendant in its First Amended Complaint in this matter on November 30, 2023. Defendant’s Original Clinical Research Protocol for the ASCENT study (the “ASCENT protocol”) is dated, August 21, 2023. Defendant amended its ASCENT protocol on October 3, 2023. Defendant began carrying out and performing the ASCENT study on December 28, 2023.

421. The ASCENT study is currently underway. In the ASCENT study, PH-ILD patients are currently being dosed with Defendant’s Proposed Product according to the ASCENT protocol.

422. The PH-ILD patients included in the ASCENT study are expected to continue taking Defendant’s Proposed Product after the completion of the study.

423. At his October 16, 2024 deposition, Defendant’s Chief Medical Officer and Rule 30(b)(6) designee Rajeev Saggar, M.D. testified as follows:

**Q.** Why is Liquidia conducting the ASCENT study?

**A.** I think it's important to allow – so first of all, Yutrepia is not a generic. We are our own branded drug. We have a formulation, a

device that is uniquely different and has properties that we believe will showcase its product profile.

424. The purpose of the ASCENT study is to generate data that Defendant can use to market Defendant's Proposed Product to healthcare providers and patients following its approval.

425. The ASCENT study is not being conducted for uses reasonably related to the development and submission of information to the FDA.

426. The ASCENT study is being conducted for purposes entirely unrelated to seeking FDA approval.

427. Defendant's Chief Medical Officer and Rule 30(b)(6) representative, Dr. Rajeev Saggur, testified at his October 16, 2024 deposition, that "ASCENT has no regulatory status in regards to the FDA's consideration for approval or indication of PH-ILD for Yutrepia."

428. Defendant instructs healthcare providers and patients enrolled in the ASCENT study to follow and abide by the ASCENT protocol.

429. [REDACTED]

[REDACTED]

[REDACTED]

430. [REDACTED]

[REDACTED]

[REDACTED]

431. The ASCENT protocol describes “cohort A” of the ASCENT study as “includ[ing] approximately 60 subjects who have WHO Group 3 Pulmonary Hypertension associated with interstitial lung disease (PH-ILD).”

[REDACTED]

[REDACTED]

[REDACTED]

435. Defendant’s Proposed Product will be administered by inhalation in the ASCENT study.

436. [REDACTED]

[REDACTED]

[REDACTED]





[REDACTED]

443.

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

453. Concrete data from the ASCENT study is not required to establish infringement of claims 2-10 and 17-19 because such data can be found in the INCREASE study that served as the basis for Defendant's regulatory and marketing strategy.

454. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

456. The healthcare providers and patients involved in the ASCENT study operate under the supervision, express instructions, and control of Defendant.

457. Institutions participating in the ASCENT study are subject to clinical trial agreements allowing Defendant to maintain substantial control over the actions of these participating institutions.

458. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**G. Defendant's Proposed Product Infringes the '327 Patent**

**1. Infringement Under the Hatch-Waxman Act**

460. Defendant's submission of its § 505(b)(2) Application to FDA infringes the asserted claims under 35 U.S.C. § 271(e)(A)(2). Specifically, Defendant has sought approval to market a drug product (Yutrepia™), the use of which is claimed by the '327 patent, prior to the expiration of the '327 patent.

461. In the Hatch-Waxman context, Defendant is bound by Defendant's Proposed Label,

and Yutrepia™—a 505(b)(2) product—assumes the properties of Tyvaso®—the RLD—with respect to the PH-ILD indication for the purposes of infringement.

462. In the Hatch-Waxman context, any differences between Yutrepia™ and Tyvaso® are immaterial to infringement as the Defendant's Proposed Label, Instructions for Use, and Packaging entirely inform what Yutrepia's™ performance is for the purposes of infringement.

463. In the Hatch-Waxman context, the uses of Yutrepia™ that are described on Defendant's Proposed Label are infringing uses if applied to PH-ILD patients.

## **2. Direct Infringement**

464. Administration of Defendant's Proposed Product by healthcare providers and/or patients according to the instructions in Defendant's Proposed Label will directly infringe claims 1-11 and 14-19 of the '327 patent.

### **a) Patients and Healthcare Providers Will Administer Yutrepia™ as Directed by Defendant's Proposed Label**

465. Defendant's Proposed Label instructs, encourages, recommends, and promotes healthcare providers and patients to use Defendant's Proposed Product in a way that infringes claims 1-11 and 14-19.

466. Healthcare providers will review, be aware of, and rely on the entirety of Defendant's Proposed Label and prescribing information/package insert prior to prescribing, administering, or instructing a patient on self-administration of Defendant's Proposed Product.

467. Healthcare providers will review the cited clinical trials in Defendant's Proposed Label, including publications, abstracts, and/or presentations related to the clinical study results relevant to the indication for which the drug will be prescribed and administered to determine if Defendant's Proposed Product is suitable for their patients.

468. Healthcare providers will understand from Defendant's Proposed Label that the

only clinical data supporting the safety and efficacy of Yutrepia™ in PH-ILD comes from Plaintiff's INCREASE study using Tyvaso®.

469. Healthcare providers will understand from Defendant's Proposed Label that Defendant and FDA expect Yutrepia™ to perform comparably in PH-ILD patients as compared to Tyvaso®, e.g., as demonstrated by the INCREASE Study.

470. Due to the express reliance of Defendant's Proposed Label healthcare providers will review Plaintiffs' publications relating to the INCREASE study—including Waxman 2021 and Nathan 2021—before prescribing Yutrepia™ to PH-ILD patients.

471. Whether or not a healthcare provider administering Defendant's Proposed Product has read Plaintiffs' publications relating to the INCREASE study, it is more likely than not that Defendant's Proposed Product will perform comparably to Tyvaso® in the INCREASE study.

472. Healthcare providers will prescribe and administer Defendant's Proposed Products to a PH-ILD patient with the intent or expectation of achieving clinical benefits that are the same or better than those reported by INCREASE, including improvements in exercise capacity, increases in 6MWD, reductions of plasma concentration of NT-proBNP, reductions in exacerbations of the interstitial lung disease, reductions of clinically worsening events due to the interstitial lung disease, and improvements in FVC.

473. Defendant's reliance on the INCREASE results and bioequivalence between Defendant's Proposed Product and nebulized Tyvaso® demonstrate that PH-ILD patients will more likely than not achieve the results of the INCREASE study following administration of Defendant's Proposed Product.

474. Healthcare providers and patients will follow the instructions of Defendant's Proposed Label.

475. Healthcare providers will instruct patients to use Defendant's Proposed Product as Defendant's Proposed Label and instructions for use describe and direct.

476. Patients will administer Defendant's Proposed Product in accordance with their healthcare provider's instructions.

477. Where a patient self-administers Defendant's Proposed Product or a healthcare provider who is not the prescribing healthcare provider administers Defendant's Proposed Product to the patient, that administration will be under the direction, supervision, and control of the prescribing healthcare provider.

478. Defendant confirmed that it is not changing the formulation for Yutrepia™, not changing its dry powder inhaler, and not changing anything that would require an update to Defendant's Proposed Label.

**b) No Measurement or Statistical Analysis Requirements**

479. The plain language of claims 2-10 and 17-19 does not require healthcare providers or patients to perform a measurement. The POSA would not understand any of claims 2-10 and 17-19 to require that healthcare providers or patients perform a measurement.

480. Defendant did not raise the issue of a measurement step or statistical analysis step as part of claim construction in this case.

481. The Court has not construed any of the Asserted Claims to require the type of measurement step or statistical analysis step that Dr. Channick suggests.

482. Regardless of whether claims 2-10 and 17-19 require a measurement, the clinical endpoints described in these claims are commonly measured and recorded by healthcare providers when treating PH-ILD patients.

483. Whether or not a healthcare provider administering Defendant's Proposed Product actually measures one or more of the clinical endpoints described in claims 2-10 and 17-19, it is



more likely than not that Defendant's Proposed Product will perform comparably to Tyvaso<sup>®</sup> in the INCREASE study. As discussed, Defendant did not perform any of its own testing of Yutrepia<sup>™</sup> in PH-ILD patients and instead relies on the safety and efficacy data from INCREASE to demonstrate how Yutrepia<sup>™</sup> would perform in these patients. The FDA accepted Liquidia's representations. As both FDA and Liquidia believe that the INCREASE results are reliable, predictive, and powered enough to reflect Yutrepia<sup>™</sup>'s real-world performance for purposes of regulatory approval, that data must be similarly reliable, predictive, and powered to reflect Yutrepia<sup>™</sup>'s real-world performance for purposes of determining direct infringement. Therefore, the POSA would understand that the results obtained following the administration of Tyvaso<sup>®</sup> will more likely than not occur in patients administered Yutrepia<sup>™</sup> according to Defendant's Proposed Label regardless of whether healthcare providers or their patients personally measured it.

484. Healthcare providers would not only seek to deliver Yutrepia<sup>™</sup> in a safe and efficacious manner, without any expectation as to how Yutrepia<sup>™</sup> will perform, including with respect to INCREASE. As discussed, the only data in the Yutrepia<sup>™</sup> label demonstrating Yutrepia<sup>™</sup> can be administered in a safe and efficacious manner to PH-ILD patients is the data from INCREASE. This would tell healthcare providers that Defendant expects Yutrepia<sup>™</sup> to produce comparable results to INCREASE when administered at the equivalent doses described in Defendant's Proposed Label. Therefore, healthcare providers administering Yutrepia<sup>™</sup> to PH-ILD patients: would be well aware of the INCREASE results, including those results found in peer-reviewed publications; would consult them prior to prescribing Yutrepia<sup>™</sup>; and would administer Yutrepia<sup>™</sup> because they expect to see similar results in their own PH-ILD patients.

485. The plain language of claims 2, 4, and 6-10 does not require healthcare providers to administer inhaled treprostinil to multiple patients, measure one of the selected parameters in

each group member, aggregate the results from the patients, and perform statistical analysis on those results.

486. The POSA would not understand any of claims 2, 4, and 6-10 to require that healthcare providers administer inhaled treprostinil to multiple patients, measure one of the selected parameters in each group member, aggregate the results from the patients, and perform statistical analysis on those results.

487. The presence or absence of statistical data on Defendant's Proposed Label is not necessary for the use of Yutrepia™ to directly infringe claims 2, 4, and 6-10 because Defendant's Proposed Label describes the INCREASE study's dosing regimen and 16-week duration.

488. The presence or absence of statistical data on Defendant's Proposed Label is not necessary for the use of Yutrepia™ to infringe claims 2, 4, and 6-10 because Defendant's Proposed Label instructs a dosing regimen that is consistent with the INCREASE study's dosing regimen.

489. Post-INCREASE, PH-ILD patients would be prescribed Yutrepia in view of significant data from the INCREASE population, on which Yutrepia's FDA approval depends. Whether or not a healthcare provider administering Defendant's Proposed Product actually performs a statistical analysis of the clinical endpoints described in claims 2, 4, and 6-10, it is more likely than not that Defendant's Proposed Product will perform comparably to Tyvaso® in the INCREASE study.

490. If claims 2, 4, and 6-10 were found to require administration of Yutrepia to more than one patient, Defendant intends to sell Yutrepia to many thousands of patients and it is not uncommon for a single healthcare provider to have many PH-ILD patients under their care at the same time. For example, Dr. Nathan treats approximately 50 PH-ILD patients annually. Therefore, if and when Yutrepia is marketed, it will be administered to a population of patients for which data

could be aggregated and analyzed.

**c) Direct Infringement of Claim 1**

491. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 1 of the '327 patent.

492. When used according to its Proposed Label, Defendant's Proposed Product will be administered to PH-ILD patients for the purpose of improving their exercise capacity.

493. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience an improvement in exercise capacity following such administration.

494. Defendant's Proposed Product, is a dry powder formulation comprising treprostinil sodium, a pharmaceutically-acceptable salt of treprostinil.

495. When used according to its Proposed Label, Defendant's Proposed Product will be administered to PH-ILD patients via inhalation.

496. When used according to its Proposed Label, Defendant's Proposed Product will be administered three to five times per day. Each of those three to five administrations is a single administration event performed by inhaling the contents of one or more capsules of Defendant's Proposed Product in two breaths.

497. When used according to its Proposed Label, Defendant's Proposed Product will be administered to PH-ILD patients in an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil sodium in a single administration event comprising at least two breaths delivering at least 6 micrograms treprostinil sodium per breath.

**d) Direct Infringement of Claim 2**

498. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 2 of the '327 patent.

499. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

500. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience a statistically significant increase in their 6MWD after 8 weeks, 12 weeks, or 16 weeks of the administering.

**e) Direct Infringement of Claim 3**

501. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 3 of the '327 patent.

502. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

503. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience an increase in their 6MWD by at least 10 meters after 8 weeks, 12 weeks, or 16 weeks of the administering.

**f) Direct Infringement of Claim 4**

504. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 4 of the '327 patent.

505. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

506. Based on the INCREASE data and Defendant's reliance on that data to market and

obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience a statistically significant reduction in their plasma concentration of N-Terminal pro B-Type Natriuretic Peptide (“NT-proBNP”) after 8 weeks, 12 weeks, or 16 weeks of the administering.

**g) Direct Infringement of Claim 5**

507. The use of Defendant’s Proposed Product according to its Proposed Label will directly infringe claim 5 of the ’327 patent.

508. As described above, administration of Defendant’s Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the ’327 patent.

509. Based on the INCREASE data and Defendant’s reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience a reduction in their plasma concentration of NT-proBNP by at least 200 pg/mL after 8 weeks, 12 weeks, or 16 weeks of the administering.

**h) Direct Infringement of Claim 6**

510. The use of Defendant’s Proposed Product according to its Proposed Label will directly infringe claim 6 of the ’327 patent.

511. As described above, administration of Defendant’s Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the ’327 patent.

512. Based on the INCREASE data and Defendant’s reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience a statistically significant reduction of at least one exacerbations of their interstitial lung disease.

**i) Direct Infringement of Claim 7**

513. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 7 of the '327 patent.

514. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

515. Defendant's Proposed Label describes a reduction in clinical worsening events "due to PH-ILD." Claim 7 requires a reduction in "clinical worsening events due to the interstitial lung disease." PH-ILD is a disease with two connected components—a pulmonary hypertension component and an interstitial lung disease component. These two components are sufficiently intertwined and worsening of one is often accompanied by worsening of the other. Further, a POSA would understand the phrase "the interstitial lung disease" as found in claim 7 to refer to the ILD component of the patient's PH-ILD, as described in claim 1. A physician reviewing the Yutrepia label would understand that the four clinical worsening events it describes could all result from worsening of the PH-ILD patient's underlying lung disease and any worsening is associated with worsening of the ILD and the PH.

516. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience a statistically significant reduction of clinical worsening events due to interstitial lung disease.

**j) Direct Infringement of Claim 8**

517. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 8 of the '327 patent.

518. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 7 of the '327 patent.

519. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience a statistically significant reduction of clinical worsening events comprising at least one of: (1) hospitalization for a cardiopulmonary indication; or (2) a decrease in their 6MWD by more than 15% as compared to their baseline 6MWD prior to the administering.

**k) Direct Infringement of Claim 9**

520. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 9 of the '327 patent.

521. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

522. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience a statistically significant improvement of their forced vital capacity ("FVC") after 8 weeks, 12 weeks, or 16 weeks of the administering.

**l) Direct Infringement of Claim 10**

523. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 10 of the '327 patent.

524. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 9 of the '327 patent.

525. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience an improvement of their

FVC by at least 20 mL after 8 weeks, 12 weeks, or 16 weeks of the administering.

**m) Direct Infringement of Claim 11**

526. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 11 of the '327 patent.

527. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

528. When used according to its Proposed Label, Defendant's Proposed Product will be administered to PH-ILD patients via inhalation using the supplied Plastiaple RS00 Inhaler.

529. The Plastiaple RS00 Inhaler is a dry powder inhalation device that provides for non-continuous inhaled drug delivery.

530. The Plastiaple RS00 Inhaler is a "pulsed inhalation device" as required by claim 11.

**n) Direct Infringement of Claim 14**

531. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 14 of the '327 patent.

532. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 11 of the '327 patent.

533. When used according to its Proposed Label, Defendant's Proposed Product will be administered to PH-ILD patients via inhalation using the supplied Plastiaple RS00 Inhaler.

534. The Plastiaple RS00 Inhaler is a dry powder inhaler that comprises a dry powder formulation containing treprostinil sodium, a pharmaceutically acceptable salt of treprostinil.

535. The Plastiaple RS00 Inhaler is a "pulsed inhalation device" as required by claim 11.

**o) Direct Infringement of Claim 15**

536. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 15 of the '327 patent.



537. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

538. When used according to its Proposed Label, Defendant's Proposed Product will be administered in a single inhalation administration event in which the patient is administered an effective amount of between 15 and 100 micrograms of treprostinil sodium.

**p) Direct Infringement of Claim 16**

539. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 16 of the '327 patent.

540. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 15 of the '327 patent.

541. When used according to its Proposed Label, Defendant's Proposed Product will be in a single inhalation administration event that delivers to the patient an effective amount of between 15 and 100 micrograms of treprostinil sodium in 15 breaths or less.

**q) Direct Infringement of Claim 17**

542. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 17 of the '327 patent.

543. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

544. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience an increase in their 6MWD by at least 10 meters after 8 weeks of the administering.

**r) Direct Infringement of Claim 18**

545. The use of Defendant's Proposed Product according to its Proposed Label will

directly infringe claim 18 of the '327 patent.

546. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

547. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience an increase in their 6MWD by at least 15 meters after 12 weeks of the administering.

**s) Direct Infringement of Claim 19**

548. The use of Defendant's Proposed Product according to its Proposed Label will directly infringe claim 19 of the '327 patent.

549. As described above, administration of Defendant's Proposed Product according to its Proposed Label meets each and every limitation of claim 1 of the '327 patent.

550. Based on the INCREASE data and Defendant's reliance on that data to market and obtain regulatory approval for Yutrepia™, it is more likely than not that PH-ILD patients administered Yutrepia™ according to its Proposed Label will experience an increase in their 6MWD by at least 15 meters after 16 weeks of the administering.

**3. Induced Infringement**

551. By marketing its Proposed Product in the United States, Defendant will induce healthcare providers and patients to directly infringe claims 1-11 and 14-19 of the '327 patent. Defendant will actively induce this direct infringement through its press releases, marketing, Proposed Label, and conduct.

552. Defendant plans to supply, market, advertise, and promote its Proposed Product with a Proposed Label that instructs and encourages healthcare providers and patients to use Defendant's Proposed Product in a manner that will infringe claims 1-11 and 14-19.

553. As discussed above, the administration of Yutrepia™ to PH-ILD patients according to Defendant's proposed label meets each and every limitation of claims 1-11 and 14-19 of the '327 patent. Defendant's Proposed Label and accompanying instructions for use will instruct, encourage, recommend, and/or promote healthcare providers and patients to use Yutrepia™ in a manner that directly infringes claims 1-11 and 14-19 of the '327 patent by healthcare providers and patients.

554. Defendant will encourage and instruct doctors and patients to administer Yutrepia™ according to the instructions in the Yutrepia label and accompanying instructions for use.

555. Defendant intends and expects that healthcare providers and patients will administer Yutrepia™ in accordance with the instructions in Defendant's Proposed Label and accompanying instructions for use.

556. Yutrepia™ and Tyvaso® are approved for the same indications, will be marketed to the same patients, and will be administered at equivalent doses.

557. As discussed above, Defendant did not provide any safety and efficacy data for Yutrepia™ in PH-ILD patients.

558. As discussed above, Defendant relied entirely on the results of the INCREASE study—as reported in the Tyvaso® label and in Plaintiff's peer-reviewed publications—to demonstrate the safety and efficacy of Yutrepia™ in PH-ILD patients.

559. As discussed above, Defendant represented to FDA that Yutrepia™ would perform comparably to Tyvaso® in PH-ILD patients. FDA accepted this representation and, as a result, did not require Defendant to conduct any human trials of Yutrepia™ in PH-ILD patients.

560. As discussed above, Defendant's Proposed Label describes certain recommended

doses of Yutrepia™ as “equivalent” to the doses of Tyvaso® used in the INCREASE study. Defendant’s Proposed Label describes how to dose Yutrepia™ in order to attain equivalent drug exposure as compared to nebulized Tyvaso®.

561. Defendant intends and expects that when administered according to its Proposed Label, Yutrepia™ will achieve comparable safety and efficacy in PH-ILD patients as compared to Tyvaso®.

562. Defendant intends to market Yutrepia™ to a large number of patients. Defendant intends and expects that when administered according to its Proposed Label, Yutrepia™ will perform comparably to what Plaintiff demonstrated for Tyvaso® in the INCREASE study, as described in the Defendant’s Proposed Label and the peer-reviewed literature describing the INCREASE study.

563. Defendant knows, intends, and expects that when Yutrepia™ is administered to PH-ILD patients according to its label, patients will likely experience the clinical benefits required by claims 2-10 and 17-19.

564. Evidence of Defendant’s intent to induce infringement can come from outside Defendant’s Proposed Label. Defendant’s marketing materials directly rely on INCREASE study data, specifically 6MWD, NT-proBNP, and clinical worsening outcomes, indicating Defendant intends for Yutrepia’s™ use to achieve these and other outcomes achieved in the INCREASE study.

565. Defendant cannot avoid infringement based on its purported subjective belief that (i) it is practicing the prior art or (ii) that the Asserted Claims are invalid. Patent infringement and invalidity are separate inquiries. The relevant inquiry is whether Defendant intentionally induces healthcare providers and patients to perform the Asserted Claims when using Yutrepia. As

discussed above, Defendant meets this requirement. Further, as discussed below, the methods of the '327 patent were not present in the public domain prior to the effective filing date of the '327 patent.

566. As discussed above, Defendant had full knowledge of the '061 application and the scope of its allowed claims when it sought to amend its § 505(b)(2) Application to add a PH-ILD indication for Yutrepia™.

567. As discussed above, Defendant knew that the allowed claims of the '061 application—which would later issue as the '327 patent—would cover the use of Yutrepia™ according to its Proposed Label.

568. Defendant has continued to seek approval of Yutrepia™ for PH-ILD even after the '327 patent issued and Plaintiff amended its complaint to assert the '327 against Defendant.

569. Defendant knows that when Yutrepia™ is administered to PH-ILD patients according to the dosing regimen and instructions in Defendant's Proposed Label, healthcare providers and/or patients will practice each and every element of claims 1-11 and 14-19 of the '327 patent.

570. Defendant knows that when Yutrepia™ is administered to PH-ILD patients according to the dosing regimen and instructions in Defendant's Proposed Label, healthcare providers and/or patients will directly infringe claims 1-11 and 14-19 of the '327 patent.

571. Defendant specifically intends to encourage, recommend, or promote infringement of claims 1-11 and 14-19 of the '327 patent by healthcare providers and patients.

#### **4. Doctrine of Equivalents**

572. To the extent that any element of any of claims 1-11 and 14-19 are not literally satisfied when Defendant's Proposed Product is administered to PH-ILD patients, all such elements are satisfied under the doctrine of equivalents.

573. As discussed above, Defendant has represented to FDA, payors, and the general public that Yutrepia™ will perform comparably to Tyvaso® when dosed to PH-ILD patients. Based on these representations, FDA did not require Defendant to perform a separate clinical trial of Yutrepia™ in human PH-ILD patients in order to establish its safety and efficacy.

574. As discussed above, Defendant's Proposed Label identifies certain doses of Yutrepia™ as "equivalent" to certain doses of Tyvaso®, including in the specific context of the INCREASE trial.

575. As discussed above, Defendant's regulatory filings for Yutrepia™ represent that the drug has comparable pharmacokinetic properties to Tyvaso®, and that as a result, patients can easily transition between the two products.

576. As discussed above, Defendant's marketing materials for Yutrepia™ rely upon the results of the INCREASE trial—which was conducted with Tyvaso®—to assert that Yutrepia™ will be safe and effective for the treatment of PH-ILD.

577. Defendant's Proposed Product and Tyvaso® perform substantially the same function in substantially the same way to achieve substantially the same result when administered to a PH-ILD patient.

## **5. Infringement by Defendant's Ongoing ASCENT Study**

578. Because the methods of administration described in the ASCENT protocol mimic the methods described in Defendant's Proposed Label, Defendant's execution of the ASCENT protocol infringes claims 1-11 and 14-19 for the same reasons as Defendant's Proposed Product.

579. Administration of Defendant's Proposed Product by healthcare providers and/or patients participating in the ASCENT study pursuant to the ASCENT protocol has directly infringed, and continues to directly infringe, claims 1-11 and 14-19 of the '327 patent.

580. Defendant has directly infringed, and continues to directly infringe, claims 1-11

and 14-19 of the '327 patent by directing, supervising, and controlling the actions of the healthcare providers and/or patients participating in the ASCENT study requiring them to strictly adhere to the ASCENT protocol.

581. Defendant's ASCENT protocol has and continues to instruct, encourage, recommend, or promote infringement of claims 1-11 and 14-19 of the '327 patent by healthcare providers and patients.

582. Based on the contents of the ASCENT protocol, Defendant specifically intends to instruct, encourage, recommend, or promote infringement of claims 1-11 and 14-19 of the '327 patent by healthcare providers and patients.

583. Defendant knows that the use of Defendant's Proposed Product according to Defendant's Proposed Label will infringe claims 1-11 and 14-19.

584. Defendant knows that the manner in which Defendant's Proposed Product is administered to PH-ILD patients in the ASCENT study mimics the dosing and administration instructions in Defendant's Proposed Label.

585. Defendant knows that administration of Defendant's Proposed Product by healthcare providers and/or patients in accordance with the ASCENT protocol will directly infringe claims 1-11 and 14-19 of the '327 patent.

586. Despite its knowledge of the '327 patent, the '061 application, and this lawsuit Defendant chose to initiate the ASCENT study and continues to undertake the ASCENT study.

587. Defendant's ASCENT study is not protected by the safe harbor provided by 35 U.S.C. § 271(e)(1). The ASCENT study is not being conducted for uses reasonably related to the development and submission of information to the FDA. The ASCENT study is being performed primarily for marketing purposes. [REDACTED]

[REDACTED]

[REDACTED]

588. The ASCENT study has, does, and will continue to infringe(d) the Asserted Claims until the study is terminated and/or the study is completed. The ASCENT study will likely result in continued infringement of the Asserted Claims because patients who participate in the ASCENT study are expected to continue using Yutrepia in accordance with the Yutrepia label even after their participation in the ASCENT study has completed. This use of Yutrepia will likely continue until Yutrepia enters the market and is sold in the United States.

## **6. Willful Infringement**

589. Defendant's conduct to date demonstrates that Defendant has acted in bad faith to deliberately and willfully infringe claims 1-11 and 14-19 of the '327 patent.

590. Defendant was closely monitoring the conduct and results of Plaintiff's INCREASE trial, including but not limited to retaining outside experts to analyze the INCREASE trial and present their findings at Advisory Board Meetings organized and paid for by Defendant.

591. As soon as the results of the INCREASE study were made public, Defendant made plans to copy and take advantage of Plaintiffs' innovative work with Tyvaso<sup>®</sup> to add a copycat PH-ILD indication for its proposed product, Yutrepia<sup>®</sup>.

592. As discussed above, Defendant, Plaintiff did not conduct any of its own clinical studies of Yutrepia<sup>™</sup> in PH-ILD and instead petitioned FDA to rely on Plaintiff's innovative and groundbreaking data from the INCREASE trial, both as disclosed in the Plaintiff's Tyvaso<sup>®</sup> labeling and Plaintiff's peer-reviewed publications. Defendant believed that it deserved to take advantage of Plaintiff's INCREASE data even though Defendant had nothing to do with conducting the study.

593. As discussed above, Defendant was closely following the '061 application during



its prosecution at the USPTO and had full knowledge of the scope of the '061 application's claims.

594. As soon as the '061 application received a notice of allowance, Defendant intentionally expedited the process of amending its § 505(b)(2) Application to copy the groundbreaking PH-ILD indication FDA had granted to Plaintiff's Tyvaso<sup>®</sup> product two years earlier.

595. The only data Defendant cited to demonstrate the safety and efficacy of Yutrepia<sup>™</sup> in PH-ILD was Plaintiff's INCREASE data for Tyvaso<sup>®</sup>.

596. [REDACTED]

[REDACTED]

[REDACTED]

597. Defendant acted with deliberate disregard for Plaintiff's patent rights when it amended its § 505(b)(2) Application to copy the PH-ILD indication by Tyvaso<sup>®</sup>.

598. Upon issuance of the '327 patent and its subsequent assertion in this action by Plaintiff, Defendant nevertheless pushed forward in adding a PH-ILD indication to Yutrepia<sup>™</sup> with full knowledge that doing so would infringe the '327 patent.

599. As discussed above, Defendant's marketing materials heavily rely on and copy Plaintiff's data from the INCREASE trial as evidence of how Yutrepia<sup>™</sup> will perform in PH-ILD patients.

600. Defendant's decision to initiate its infringing ASCENT clinical trial after the '327 patent was asserted by Plaintiff in this action is evidence of Defendant's bad faith.

601. Defendant's decision to submit and rely on non-infringement opinions from its clinical expert, Dr. Richard Channick, [REDACTED] Defendant's marketing materials, Defendant's Proposed Label, and [REDACTED]

Rule 30(b)(6) representative and Chief Medical Officer, Rajeev Saggar, is evidence of Defendant's bad faith.

602. Defendant's assertion of a legally-defunct "practicing the prior art" defense against Plaintiff's allegations of induced infringement in this action is evidence of Defendant's bad faith.

603. Defendant's continued assertion of a baseless inequitable conduct counterclaim, along with the continued changes and attempted changes to that theory—despite the obligation to plead it with particularity at the pleadings stage—is evidence of Defendant's bad faith.

604. Defendant's deliberate engagement of outside consultants who are concurrently engaged by Plaintiff—including Dr. Rajan Saggar—is evidence of Defendant's bad faith. Defendant's engagement of Dr. Rajan Saggar to provide advice on how Yutrepia™ could be distinguished in the marketplace from Tyvaso® while Dr. Saggar was concurrently engaged by Plaintiff is further evidence of Defendant's bad faith.

605. Defendant's outside counsel's representation of Dr. Rajan Saggar for purposes of this litigation while Dr. Saggar was actively engaged as a consultant by, and had active confidentiality obligations to, Plaintiffs is evidence of Defendant's bad faith.

## **V. FACTS PERTAINING TO VALIDITY OF THE '327 PATENT**

### **A. Priority Date**

606. At least claims 1, 2, 6-11, and 14-16 of the '327 patent are entitled to claim priority to the '810 Provisional, filed on April 17, 2020.

607. A POSA reading the disclosures of the '810 Provisional would have understood that as of April 17, 2020 the inventors were in possession of the inventions described in at least claims 1, 2, 6-11, and 14-16 of the '327 patent.

608. A POSA reading the disclosures of the '810 Provisional would have understood that as of April 17, 2020 the inventions described in at least claims 1, 2, 6-11, and 14-16 of the

'327 patent could be practiced without undue experimentation.

**1. Disclosures of the '810 Provisional**

609. The '810 Provisional, is the first application to which the '327 patent claims priority and lists the same inventors as the '327 patent.

610. A POSA would have understood that the clinical results reported in Example 1 of the '810 Provisional came from UTC's INCREASE study at least because: (1) the efficacy endpoints and duration of treatment are reflective of a PH study; (2) the listed inventors on the '810 Provisional are associated with UTC; and (3) there were numerous parallels between Example 1 and public information regarding the INCREASE study.

611. As of April 17, 2020, the INCREASE study was the only large-scale, placebo-controlled study that had been conducted using inhaled treprostinil in PH-ILD patients. At this time, the study protocols for INCREASE were a matter of public record, but its results had not been published in the scientific literature.

612. A POSA would have understood that the administration of inhaled treprostinil to PH-ILD patients in Example 1 of the '810 Provisional was intended to improve the exercise capacity in those patients.

613. A POSA would have understood that the '810 Provisional describes improving exercise capacity in PH-ILD patients with inhaled treprostinil by improving symptoms such as shortness of breath and fatigue.

614. Examples 1 and 2 of the '810 Provisional contain identical disclosures to Examples 1 and 2 of the as-issued specification of the '327 patent.

615. A POSA would have understood from the absolute and percent predicted FVC data reported in Example 1 of the '810 Provisional that PH-ILD patients treated with inhaled treprostinil improved their exercise capacity:

Visit	Treatment	N	LS Mean	Contrast	Estimated Difference	95% CI	p-value
FVC (mL)							
Week 8	Inhaled treprostinil	142	5.49	Inhaled treprostinil - Placebo	28.47	-30.81, 87.74	0.3453
	Placebo	141	-22.98				
Week 16	Inhaled treprostinil	130	9.77	Inhaled treprostinil - Placebo	44.40	-25.25, 114.05	0.2106
	Placebo	126	-34.63				
FVC (% predicted)							
Week 8	Inhaled treprostinil	142	0.77	Inhaled treprostinil - Placebo	1.79	0.37, 3.21	0.0139
	Placebo	141	-1.02				
Week 16	Inhaled treprostinil	130	1.07	Inhaled treprostinil - Placebo	1.80	0.20, 3.39	0.0277
	Placebo	126	-0.72				

Abbreviations: CI, confidence interval; FVC, forced vital capacity; ITT, Intent-to-Treat; LS, least square; MMRM, mixed model repeated measurement  
LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Visit	Treatment	N	LS Mean	Contrast	Estimated Difference	95% CI	p-value
PH-ILD Etiology: IIP							
FVC (mL)							
Week 8	Inhaled treprostinil	58	9.27	Inhaled treprostinil - Placebo	46.48	-32.55, 125.51	0.2467
	Placebo	71	-37.21				
Week 16	Inhaled treprostinil	52	22.16	Inhaled treprostinil - Placebo	108.18	15.25, 201.10	0.0229
	Placebo	63	-86.02				
FVC (% predicted)							
Week 8	Inhaled treprostinil	58	0.92	Inhaled treprostinil - Placebo	1.95	0.12, 3.79	0.0373
	Placebo	71	-1.03				
Week 16	Inhaled treprostinil	52	1.66	Inhaled treprostinil - Placebo	2.88	0.72, 5.05	0.0096
	Placebo	63	-1.23				

Abbreviations: CI, confidence interval; CPFE, combined pulmonary fibrosis and emphysema; CTD, connective tissue disease; FVC, forced vital capacity; ILD, interstitial lung disease; IIP, idiopathic interstitial pneumonia; ITT, Intent-to-Treat; LS, least square; MMRM, mixed model repeated measurement

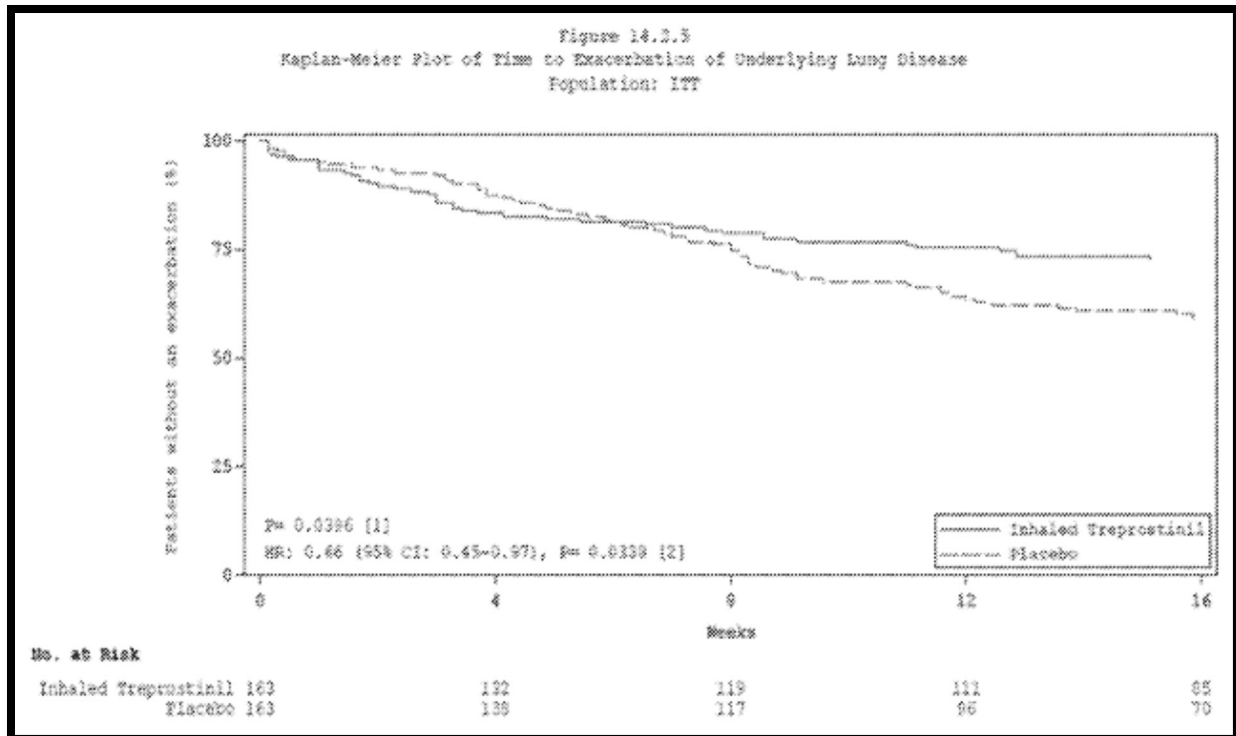
LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

IPF							
FVC (mL)							
Week 8	Inhaled treprostinil	31	41.69	Inhaled treprostinil - Placebo	84.522	-20.409, 189.454	0.1128
	Placebo	47	-42.83				
Week 16	Inhaled treprostinil	28	38.24	Inhaled treprostinil - Placebo	168.524	40.078, 296.970	0.0108
	Placebo	42	-130.3				
FVC (% predicted)							
Week 8	Inhaled treprostinil	31	1.60	Inhaled treprostinil - Placebo	2.543	0.145, 4.941	0.0380
	Placebo	47	-0.94				
Week 16	Inhaled treprostinil	28	1.62	Inhaled treprostinil - Placebo	3.504	0.712, 6.295	0.0147
	Placebo	42	-1.88				

Abbreviations: CI, confidence interval; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; ITT, Intent-to-Treat; LS, least square; MMRM, mixed model repeated measurement  
LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

616. A POSA would have understood from the exacerbations data reported in Example 1 of the '810 Provisional that PH-ILD patients treated with inhaled treprostinil improved their exercise capacity:

[0083] Treatment resulted in significantly fewer exacerbations of underlying lung disease over the 16-week treatment period (26.4% in Inhaled Treprostinil group and 38.7% in placebo group;  $p=0.018$ ) and decreased risk of an exacerbation of underlying lung disease (hazard ratio 0.66 or 34% reduction in risk) as shown in FIG. 1.



617. A POSA would have understood from the comparison of inhaled treprostinil to nintedanib and pirfenidone reported in Example 1 of the '810 Provisional that PH-ILD patients treated with inhaled treprostinil improved their exercise capacity:

Nintedanib: IPF ~ 109 mL (3.2% predicted) at 52 weeks

Pirfenidone: IPF ~ 153-193 mL at 52 weeks

618. A POSA would have understood that prior to the disclosures of the '810 Provisional no drug had ever been able to maintain or improve FVC values in ILD.

619. The fact that FVC was originally incorporated into the INCREASE study as a "safety endpoint" does not mean that the results UTC subsequently obtained for this endpoint

during the trial do not have any relevance to efficacy measures in that study, such as exercise capacity. The FVC data obtained from INCREASE were groundbreaking and profoundly surprising to both those in the field and the inventors themselves. As discussed above, this was the first time a drug had ever shown improvements in FVC in the context of ILD. In fact, a POSA would understand that FVC is commonly used as a primary efficacy endpoint in large clinical trials for ILD therapies. A POSA would therefore not discount the impact of the groundbreaking FVC data reported in Example 1 of the '810 Provisional Application simply because it was labelled as a "safety endpoint" for purposes of the INCREASE trial. Rather, a POSA would thoroughly examine this data in the context of the existing literature, and as discussed above, conclude that the observed improvements in FVC would be accompanied by an improvement in exercise capacity.

620. A POSA would have understood from the prophetic Example 2 of the '810 Provisional that the inventors were confident in the clinical significance of the data reported in Example 1 of the '810 Provisional.

621. A POSA would have understood from the '810 Provisional that the PH-ILD patients in Example 1 were administered inhaled treprostinil at a starting dose of 3 breaths (18 mcg) four times a day, which was titrated to a maximum of 12 breaths (72 mcg), as tolerated. A POSA would have understood this titration procedure is a common clinical practice for determining a maximum tolerated dose.

622. A POSA would have understood from the statistically significant FVC and exacerbation data reported in Example 1 of the '810 Provisional that the PH-ILD patients administered inhaled treprostinil also experienced a statistically significant improvement in 6MWD after 8, 12, or 16 weeks.

623. A POSA would have understood that the '810 Provisional disclosed medically recognized techniques by which ILD exacerbations can be evaluated.

624. A POSA would have understood from the exacerbation data in Example 1 of the '810 Provisional that treatment with inhaled treprostinil resulted in significantly fewer exacerbations of underlying lung disease in patients compared to placebo.

625. A POSA would have understood from Figure 1 of the '810 Provisional that treatment with inhaled treprostinil resulted in a statistically significant reduction of ILD exacerbations versus placebo.

626. A POSA would have understood that the statistically significant FVC and exacerbations data reported in Example 1 of the '810 Provisional would be accompanied by a statistically significant reduction in clinical worsening.

627. A POSA would have understood that the statistically significant decrease in acute exacerbations reported in Example 1 of the '810 Provisional would be accompanied by a reduction in hospitalizations for cardiopulmonary indication.

628. A POSA would have understood that the statistically significant improvement in FVC reported in Example 1 of the '810 Provisional would be accompanied by a reduction in the instances of patients experiencing a 15% reduction in 6MWD.

629. A POSA would have understood that the '810 Provisional discloses how absolute FVC and percent predicted FVC can be measured and increased in patients treated with inhaled treprostinil.

630. A POSA would have understood from Example 1 of the '810 Provisional that all groups of PH-ILD patients showed improvements in absolute FVC at the 8 and 16 week timepoints.

631. A POSA would have understood from Example 1 of the '810 Provisional that the IIP and IPF PH-ILD subpopulations showed statistically significant improvements in absolute FVC at the 16 week timepoint.

632. A POSA would have understood from Example 1 of the '810 Provisional that all groups of PH-ILD patients showed statistically significant improvements in percent predicted FVC at the 8 and 16 week timepoints.

633. A POSA would have understood that the statistically significant percent predicted FVC results reported in Example 1 of the '810 Provisional were based on underlying changes in absolute FVC.

634. A POSA would have understood from the FVC data reported for week 8 and week 16 in Example 1 of the '810 Provisional that there would also be a statistically significant increase in FVC at week 12.

635. A POSA would have understood from the FVC data reported in Example 1 of the '810 Provisional that all groups of PH-ILD patients experienced an increase in absolute FVC in excess of 20 mL following administration of inhaled treprostinil after 8, 12, or 16 weeks.

636. A POSA would have understood from the absolute FVC data for the IIP and IPF PH-ILD subpopulations reported in Example 1 of the '810 Provisional that the inventors were in possession of improving absolute FVC by at least 20 mL in PH-ILD patients following administration of inhaled treprostinil after 8, 12, or 16 weeks.

637. A POSA would have understood from the disclosures at [0048] and [0060] of the '810 Provisional and the reference to U.S. Patent No. 9,339,507, PCT/US2017/031301 and PCT/US2013/072647 that inhaled treprostinil could be administered to PH-ILD patients non-continuously, including through the use of a dry powder inhaler.



638. A POSA would have understood from Example 1 of the '810 Provisional that nebulizers deliver drugs to patients in a non-continuous manner and that the operation of patients taking multiple breaths per treatment session indicated that inhaled treprostinil is delivered non-continuously.

639. A POSA would have understood from the disclosures at [0048] and [0060] of the '810 Provisional that inhaled treprostinil could be dosed to PH-ILD patients with a dry powder inhaler. Moreover, [0060] of the '810 Provisional provides a real world example of a treprostinil dry powder formulation delivered with a breath-powered dry powder inhaler.

640. A POSA would have understood that the dry powder inhalers disclosed in the '810 Provisional are pulsed inhalation devices because they provide for non-continuous delivery of inhaled treprostinil.

641. A POSA would have understood from the dosing schedule reported in Example 1 of the '810 Provisional that patients were administered an effective amount of treprostinil of 18-72 mcg per inhalation administration event.

642. A POSA would have understood from the dosing schedule reported in Example 1 of the '810 Provisional that the patients in the study did not exceed 15 breaths of treprostinil per single inhalation administration event.

## **2. Background Knowledge of a POSA Regarding FVC**

643. A POSA in April 2020 would not have knowledge of deposition testimony provided by the named inventors of the '327 patent in 2024.<sup>1</sup>

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<sup>1</sup> At her 2024 deposition, named inventor Leigh Peterson testified that she and the inventors did not see the FVC data from INCREASE until *after* they had already reviewed the 6MWD data from the same study. Dr. Peterson additionally testified that she believed there to be an “indirect relation” between FVC and exercise capacity due to the “multifactorial” mechanism of action of treprostinil.

644. As of April 17, 2020, it was well established from registry data that clinical outcomes are worse for PH-ILD patients than in for PAH patients precisely because of the additional lung pathophysiology that is involved with PH-ILD.

645. A POSA would also know that organ systems and tissues do not operate in a vacuum; rather, they operate as an interconnected network that is often complex and unpredictable. In a disease like PH-ILD, the lung pathophysiology, e.g., the loss of lung parenchyma due to fibrosis, necessarily impacts pulmonary vascular function—and potentially, vice-versa. For example, a POSA would know that the relentless destruction of lung parenchyma in progressive fibrotic lung diseases is associated with loss of pulmonary microvasculature, and a POSA would know that this pathophysiology and pathobiology is implicated in PH-ILD. A POSA would similarly understand PH is nearly an inevitable consequence when the lung parenchyma is destroyed at a rate that is typical for progressive fibrotic ILD.

646. A POSA would know that FVC is a well-established means of monitoring the destruction of lung function in ILD and would further appreciate exacerbations' role in accelerating this lung function.

647. A POSA would have understood that as of April 17, 2020 numerous publications such as those listed below linked changes in FVC to changes in exercise capacity:

- Swigris J.J., The 6 Minute Walk in Idiopathic Pulmonary Fibrosis: Longitudinal Changes and Minimum Important Difference, 65(2) THORAX 173 (2010) (“Swigris 2010”).
- Du Bois R *et al.*, *Six-Minute-Walk Test in Idiopathic Fibrosis*, 183(9) AM. J. RESPIR. CRIT. CARE MED. 1231 (2010) (“du Bois 2010”).
- Du Bois R.M. *et al.*, Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis: Test Properties and Minimal Clinically Important Difference. 184(12) AM. J. RESPIR. CRIT.

CARE 1382 (2011) (“du Bois 2011”).

- Nathan S et al., Validation of Test Performance Characteristics and Minimal Clinically Important Difference of the 6-Minute Walk Test in Patients with Idiopathic Pulmonary Fibrosis, 109(7) RESPIR. MED. 914 (2015) (“Nathan 2015”).
- Nishiyama O. et al., Pulmonary Hemodynamics and Six-Minute Walk Test Outcomes in Patients with Interstitial Lung Disease, CAN. RESPIR. J. (2016) (“Nishiyama 2016”).
- Brown A.W. and Nathan S.D., The Value and Application of the 6-Minute-Walk Test in Idiopathic Pulmonary Fibrosis, 15(1) ANN. AM. THORAC. SOC. 3 (2018) (“Brown 2018”).
- Fell C.D. et al., The Prognostic Value of Cardiopulmonary Exercise Testing in Idiopathic Pulmonary Fibrosis, 179(5) AM. J. RESPIR. CRIT. CARE MED. 402, 403 (2009) (“Fell 2009”).
- Wallaert B. et al., Reduction of Maximal Oxygen Uptake in Sarcoidosis: Relationship with Disease Severity, 82(6) RESPIRATION 501 (2011) (“Wallaert 2011”).
- Pastré J. et al., Determinants of exercise capacity in cystic fibrosis patients with mild-to-moderate lung disease, B.M.C. PULM. MED. 14, 74 (2014) (“Pastré 2014”).
- Oldham W.M. et al., Network Analysis to Risk Stratify Patients with Exercise Intolerance, 122(6) CIRC. RES. 864 (2018) (“Oldham 2018”).

648. A POSA would have understood that a correlation between improvements in FVC and improvements in exercise capacity made intuitive sense in the context of PH-ILD.

649. A POSA would have understood that acute exacerbations of lung disease are typically associated with decline in functional health of PH-ILD patients requiring medical intervention.

650. A POSA would have understood that PH-ILD patients treated with inhaled

treprostinil experiencing fewer exacerbations of underlying lung disease as compared to placebo would experience an accompanying improvement in exercise capacity.

651. A POSA would have understood that the Tyvaso nebulizer system delivers 6 mcg of treprostinil per breath.

652. A POSA would have understood that Swigris 2010, du Bois 2010, du Bois 2011, Nathan 2015, Nishiyama 2016, and Brown 2018 disclosed study results where FVC is correlated with 6MWD.

653. A POSA would have understood that PH-ILD patients who experience an acute exacerbation of ILD often face serious adverse consequences such as hospitalization, significant reductions in exercise capacity, loss of lung function and death, which a POSA would understand to constitute clinical worsening events.

654. A POSA would have understood that acute exacerbations of ILDs such as IPF are associated with dismal outcomes and that about half of all IPF deaths are preceded by acute exacerbations.

655. A POSA would have understood that acute exacerbations of ILD typically result in hospitalizations for PH-ILD patients and that a hospitalization in this context is for a cardiopulmonary indication.

656. A POSA would have understood that a change in percent predicted FVC is the most valuable expression of FVC in the context of large clinical trials because it allows for patients of varying demographics to be compared against each other.

657. A POSA would have understood that the IIP subgroup is the largest general category of PH-ILD and that IPF is the largest subset of the IIP subgroup.

658. A POSA would have understood that a pulsed inhalation device can be a dry

powder inhaler.

659. A POSA would have understood that with respect to UTC's Tyvaso nebulizer, when a patient takes a set number of breaths during a single dosing session, that dosing session would be a single inhalation administration event.

660. A POSA treating PH-ILD would have taken note of the publications below, which demonstrate the efficacy and safety of antifibrotic medications for IPF and progressive fibrotic ILDs, and all of which discuss the effect of the applicable active ingredient on FVC and 6MWD. A POSA would understand that the data available prior to April 17, 2020 from these publications suggest that antifibrotic medications appear to decrease the frequency of acute exacerbations and improve the rate of FVC decline:

- CAPACITY – Noble P.W. et al., Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (CAPACITY): Two Randomised Trials, 377 LANCET 1760 (2011).
- ASCEND – King T.E. Jr., A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis, 370(22) N. ENGL. J. MED. (2014).
- INPULSIS-1 & INPULSIS-2 – Richeldi L. et al., *Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis*, 370(22) N. ENGL. J. MED. 2071 (2014).
- INBUILD – Flaherty 2019 – Flaherty K. et al., *Nintedanib in Progressive Fibrosing Interstitial Lung Diseases*, 381(18) N. ENGL. J. MED. (2019).

661. A POSA would have understood from the CAPACITY trial that a reduction in decline in FVC is correlated with a reduction in decline in 6MWD in IPF patients.

662. A POSA would have understood from the ASCEND trial that a reduction in decline in FVC is correlated with a reduction in decline in 6MWD in IPF patients.

663. A POSA would have understood from Fell 2009 that percent predicted FVC

correlates with VO<sub>2</sub>max in IPF patients.

664. A POSA would have understood from Swigris 2010 that there is a statistically significant trend between an improvement in percent predicted FVC and an improvement in 6MWD in IPF patients.

665. A POSA would have understood from Wallaert 2011 that FVC correlates with VO<sub>2</sub> peak in sarcoidosis patients.

666. A POSA would have understood from du Bois 2010 and du Bois 2011 that there is a statistically significant correlation between 6MWD and percent predicted FVC, and a stronger correlation between change in 6MWD and change in percent predicted FVC, for IPF patients.

667. A POSA would have understood from Nathan 2015 that there is a statistically significant trend between change in percent predicted FVC and change in 6MWD in IPF patients.

668. A POSA would have understood from Oldham 2018 that FVC is a key predictor of VO<sub>2</sub> peak.

669. A POSA would have understood from Nishiyama 2016 that there is a statistically significant trend between both absolute FVC and percent predicted FVC and 6MWT outcomes in ILD patients.

670. A POSA would have understood from Brown 2018 that 6MWT distance is associated with percent predicted FVC in IPF patients.

671. A POSA would have understood from Pastre 2014 that percent predicted FVC is associated with peak VO<sub>2</sub> in cystic fibrosis patients.

672. A POSA would have understood from Carter R. *et al.*, *Predicting Oxygen Uptake for Men and Women with Moderate to Severe Chronic Obstructive Pulmonary Disease*, 84(8) Arch. Phys. Med. Rehabil. 1158 (2003) (“Carter 2003”) that FVC is correlated with exercise

capacity in COPD patients.

673. A POSA would have understood that while a positive change in FVC would lead a POSA to expect a positive change in exercise capacity, the opposite is not necessarily true, i.e., a POSA would not necessarily understand it to be true that a positive change in exercise capacity would be associated with a positive change in FVC.

674. A POSA would have understood that exercise capacity is determined by many variables and that FVC is one determinant of exercise capacity and does not necessarily account for all the other factors that contribute to exercise capacity such that there are clinical situations where a patient's exercise capacity will improve but their FVC will not.

675. A POSA would have understood that unlike a bi-directional mathematical correlation, two variables can be correlated in a single direction in a clinical context.

676. A POSA would have understood that a patient could be subjected to a method that increases exercise capacity while simultaneously increasing acute exacerbations making the patient sicker resulting in no statistically significant increase in FVC.

### **3. Priority Support for Asserted Claims of the '327 Patent**

#### **a) Claim 1**

677. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 1 of the '327 patent and that claim 1 of the '327 patent could be practiced without undue experimentation.

678. As discussed above, a POSA would have understood from the '810 Provisional that the PH-ILD patients in Example 1 were administered inhaled treprostinil at a starting dose of 3 breaths (18 mcg) four times a day, which was titrated to a maximum of 12 breaths (72 mcg), as tolerated. A POSA would have understood this dosing regimen to encompass administering inhaled treprostinil in an effective amount of at least 15 mcg up to a maximum tolerated dose in a

single administration event comprising at least 6 mcg per breath.

679. As discussed above, the '810 Provisional disclosed that, when administered to PH-ILD patients, inhaled treprostinil was shown to improve symptoms such as shortness of breath and fatigue.

680. As discussed above, Example 1 of the '810 Provisional disclosed that, as compared to placebo, the PH-ILD patients who were administered inhaled treprostinil exhibited both (i) a statistically significant improvement in percent predicted FVC; and (ii) a statistically significant decrease in exacerbations of their underlying ILD. As discussed above, a POSA would have understood those improvements to have been correlated with improvements in exercise capacity.

681. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of a method of using inhaled treprostinil to improve exercise capacity in PH-ILD patents.

682. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that exercise capacity could be improved in patients having PH-ILD by administering inhaled treprostinil in an effective amount of at least 15 mcg up to a maximum tolerated dose in a single administration event comprising at least 6 mcg per breath.

**b) Claim 2**

683. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 2 of the '327 patent and that claim 2 of the '327 patent could be practiced without undue experimentation.

684. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 1 of the '327 patent and that claim 1 of the '327 patent could be practiced without undue experimentation.

685. As described above, Example 1 of the '810 Provisional disclosed that, as compared



to placebo, the PH-ILD patients who were administered inhaled treprostinil exhibited both (i) a statistically significant improvement in percent predicted FVC; and (ii) a statistically significant decrease in exacerbations of their underlying ILD. A POSA would have understood those improvements to have been accompanied by a corresponding statistically significant improvements in exercise capacity. A POSA would further understand that this improvement in exercise capacity would be reflected in an improvement in 6MWD, a widely accepted measure of exercise capacity. This understanding would be supported by the prior art literature, discussed above, which demonstrate a correlation between improvements in FVC and improvements in 6MWD.

686. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD consistent with the method of claim 1 of the '327 patent would result in a statistically significant improvement in 6MWD after 8, 12, or 16 weeks.

**c) Claim 6**

687. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 6 of the '327 patent and that claim 6 of the '327 patent could be practiced without undue experimentation.

688. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 1 of the '327 patent and that claim 1 of the '327 patent could be practiced without undue experimentation.

689. As described above, Example 1 of the '810 Provisional disclosed that, as compared to placebo, the PH-ILD patients who were administered inhaled treprostinil exhibited a statistically significant decrease in exacerbations of their underlying ILD.

690. A POSA reading the '810 Provisional as of April 17, 2020 would have understood

that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent would result in a statistically significant reduction of at least one exacerbations of ILD.

**d) Claim 7**

691. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 7 of the '327 patent and that claim 7 of the '327 patent could be practiced without undue experimentation.

692. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 1 of the '327 patent and that claim 1 of the '327 patent could be practiced without undue experimentation.

693. As described above, Example 1 of the '810 Provisional disclosed that, as compared to placebo, the PH-ILD patients who were administered inhaled treprostinil exhibited a statistically significant decrease in exacerbations of their underlying ILD.

694. As discussed above, a POSA would understand that when a PH-ILD patient experiences an acute exacerbation of underlying lung disease, there are often serious adverse consequences including hospitalization, significant reductions in exercise capacity, loss of lung function, and even death. A POSA would understand these and similar adverse events to constitute “clinical worsening” for purposes of claim 7 of the '327 patent.

695. A POSA would understand that if PH-ILD patients improved their FVC while reducing their incidence of acute exacerbations, these changes would be accompanied by a corresponding statistically significant reduction in clinical worsening. This is especially the case with respect to the reduction in exacerbations, which, a POSA would understand to often be the direct cause of clinical worsening events in PH-ILD patients

696. A POSA reading the '810 Provisional as of April 17, 2020 would have understood

that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent would result in a statistically significant reduction of clinical worsening events due to ILD.

**e) Claim 8**

697. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 8 of the '327 patent and that claim 8 of the '327 patent could be practiced without undue experimentation.

698. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claims 1 and 7 of the '327 patent and that claims 1 and 7 of the '327 patent could be practiced without undue experimentation.

699. As discussed above, a POSA would understand that acute exacerbations of underlying lung disease typically result in hospitalizations for PH-ILD patients. A POSA would further understand hospitalization in this context to be for a "cardiopulmonary indication," i.e., PH-ILD. Thus, because Example 1 of the '810 Provisional provides data demonstrating a statistically significant decrease in acute exacerbations in patients receiving inhaled treprostinil, a POSA would understand this to be accompanied by a reduction in "hospitalization for cardiopulmonary indication," as required by claim 8 of the '327 patent.

700. As discussed above, a POSA would understand from Example 1 of the '810 provisional that the reported statistically significant improvement in percent predicted FVC across the patient population would be accompanied by a corresponding improvement in exercise capacity, e.g., as reflected by increased 6MWD. Because a POSA would understand that the administration of inhaled treprostinil would improve a patient's 6MWD, a POSA would understand that the patient would be less likely to experience a 15% reduction in walk distance. Similarly, a POSA would understand that reductions in 6MWD are often correlated with

corresponding reductions in FVC. A POSA would therefore understand from the FVC data reported in Example 1 that patients would experience fewer instances of their 6MWD being reduced by 15%.

701. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD consistent with the method of claim 1 of the '327 patent would result in a statistically significant reduction of clinical worsening events due to ILD where the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in 6MWD by more than 15% compared to baseline.

**f) Claim 9**

702. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 9 of the '327 patent and that claim 9 of the '327 patent could be practiced without undue experimentation.

703. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 1 of the '327 patent and that claim 1 of the '327 patent could be practiced without undue experimentation.

704. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD patients disclosed therein resulted in all patient populations exhibiting a statistically significant improvement in percent predicted FVC after 8 and 16 weeks of treatment.

705. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD patients disclosed therein resulted in the PH-IIP and PH-IPF patient populations exhibiting a statistically significant improvement in absolute FVC after 16 weeks of treatment. These subpopulations represent approximately 43% and 27% of the study patient population with reported FVC results, respectively, which a POSA

would understand to be consistent with IIP being the largest general category of ILD and IPF in turn being the largest subset of IIP.

706. A POSA would understand that in the context of the clinical trial described in Example 1 of the '810 Provisional, percent predicted FVC would be a preferable way to express the FVC data because it normalizes the change in FVC for every individual patient's underlying physiology.

707. A POSA trying to determine whether the inventors possessed a treatment method that would produce statistically significant improvement in FVC as required by claim 9 of the '327 patent, would primarily look to the percent predicted expression of FVC data, not the presentation of that same data in terms of absolute volume.

708. To the extent a statistically significant improvement in both absolute FVC and percent predicted FVC is required to demonstrate that the inventors were in possession of the invention described in claim 9 of the '327 patent, a POSA would understand that the '810 Provisional clearly identifies which particular embodiments of claim 9 of the '327 patent are operable—i.e., the IIP and IPF subpopulations at week 16—and provides supporting data for these embodiments. In this scenario, a lack of statistically significant improvement in absolute FVC for other embodiments of the claim would not cause a POSA to conclude that the inventors lacked possession of the method described in claim 9 of the '327 patent.

709. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent would result in a statistically significant improvement of FVC after 8, 12, or 16 weeks.

**g) Claim 10**

710. A POSA reading the '810 Provisional as of April 17, 2020 would have understood

that the inventors were in possession of claim 10 of the '327 patent and that claim 10 of the '327 patent could be practiced without undue experimentation.

711. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claims 1 and 9 of the '327 patent and that claims 1 and 9 of the '327 patent could be practiced without undue experimentation.

712. A POSA reading claim 10 of the '327 patent would understand claim 10 of the '327 patent to require a 20 mL improvement in absolute FVC after 8 weeks, 12 weeks, or 16 weeks of treatment, but would not understand the claim to require that this 20 mL improvement be statistically significant.

713. As discussed above, Example 1 of the '810 provisional disclosed that across all patient populations, PH-ILD patients administered inhaled treprostinil exhibited an improvement in their absolute FVC after both 8 and 16 weeks as compared to placebo. Further, these improvements in absolute FVC were statistically significant at the 16 week time point for the PH-IIP and PH-IPF populations.

714. To the extent a statistically significant improvement in absolute FVC is required to demonstrate that the inventors were in possession of the invention described in claim 10 of the '327 patent, a POSA would understand that the '810 Provisional clearly identifies which particular embodiments of claim 10 of the '327 patent are operable—i.e., the IIP and IPF subpopulations at week 16—and provides supporting data for these embodiments. In this scenario, a lack of statistically significant improvement in absolute FVC for other embodiments of the claim would not cause a POSA to conclude that the inventors lacked possession of the method described in claim 10 of the '327 patent.

715. A POSA reading the '810 Provisional as of April 17, 2020 would have understood

that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent would result in both (i) a statistically significant improvement in FVC; and (ii) an improvement in absolute FVC of at least 20 mL after 8, 12, or 16 weeks.

**h) Claim 11**

716. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 11 of the '327 patent and that claim 11 of the '327 patent could be practiced without undue experimentation.

717. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 1 of the '327 patent and that claim 1 of the '327 patent could be practiced without undue experimentation.

718. As discussed above, the '810 Provisional discloses the administration of inhaled treprostinil to PH-ILD patients using a pulsed inhalation device.

719. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent could be performed with a pulsed inhalation device.

**i) Claim 14**

720. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 14 of the '327 patent and that claim 14 of the '327 patent could be practiced without undue experimentation.

721. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claims 1 and 11 of the '327 patent and that claims 1 and 11 of the '327 patent could be practiced without undue experimentation.

722. As discussed above, the '810 Provisional discloses the administration of inhaled treprostinil to PH-ILD patients using a pulsed inhalation device that is a dry power inhaler

delivering a dry powder formulation of treprostinil.

723. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent could be performed with a pulsed inhalation device that is a dry power inhaler delivering a dry powder formulation of treprostinil.

**j) Claim 15**

724. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 15 of the '327 patent and that claim 15 of the '327 patent could be practiced without undue experimentation.

725. As described above, a POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 1 of the '327 patent and that claim 1 of the '327 patent could be practiced without undue experimentation.

726. As described above, the PH-ILD patients in the active arm of Example 1 of the '810 Provisional were administered inhaled treprostinil at a starting dose of 3 breaths (18 mcg) four times a day, which was titrated to a maximum of 12 breaths (72 mcg), as tolerated.

727. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent could be performed with an effective amount of treprostinil from 15 mcg to 100 mcg in a single inhalation administration event.

**k) Claim 16**

728. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the inventors were in possession of claim 16 of the '327 patent and that claim 16 of the '327 patent could be practiced without undue experimentation.

729. As described above, a POSA reading the '810 Provisional as of April 17, 2020



would have understood that the inventors were in possession of claims 1 and 15 of the '327 patent and that claims 1 and 15 of the '327 patent could be practiced without undue experimentation.

730. As described above, the PH-ILD patients in the active arm of Example 1 of the '810 Provisional were administered between 3 and 12 breaths of inhaled treprostinil as tolerated.

731. A POSA reading the '810 Provisional as of April 17, 2020 would have understood that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent could be performed with an effective amount of treprostinil from 15 mcg to 100 mcg in a single inhalation administration event not exceeding 15 breaths.

**B. Inventorship**

732. Leigh Peterson, Peter Smith, and Chunqin Deng are the only inventors of the '327 patent.

733. When the final INCREASE protocol was adopted on February 15, 2017, no one, including the INCREASE steering committee, had a definite and permanent idea of the method later claimed in the '327 patent.

734. Conception of the claimed invention of the '327 patent was not possible until the INCREASE data was unblinded and analyzed by Leigh Peterson, Peter Smith, and Chunqin Deng. Peter Smith testified that he and others at UTC had doubts concerning the success of the INCREASE study before patients were enrolled and the unblinding of the results:

Q. Did you or anyone else at UTC have doubts that the INCREASE trial would be successful?

A. Yes.

Q. Can you explain that a little bit?

A. Well, there was a lot of failed studies, very sick patient population, and so it was – you know, we had data monitoring committee meetings on a regular basis, and given the prior history with some of the safety concerns with other PAH therapies there was

absolutely some concern as to whether or not we would have a safe and effective therapy. And so for sure it was absolutely far from a sure thing.

735.

[REDACTED]

736.

[REDACTED]

737. Dr. Deng also provided testimony concerning his doubts about the success of the INCREASE study and why the results were unexpected:

Q. What discussions do you recall with the steering committee following the unblinding of the data in the INCREASE study?

A. We made slides. We made slides, presented to them.

Q. What was in the slides that you presented to the steering committee?

A. The INCREASE study trial result.

Q. And do you recall any reaction by the steering committee member to this presentation to them of the results

A. They were excited. Very happy.

Q. Why were they excited?

A. Because there's no approved therapy for the Group 3, so this would be the -- actually, a lot of PAH drugs have been tested in WHO Group 3 than PH-ILD patients. It all failed either due to the efficacy issue or due to the safety issue. So this would be the first study actually demonstrate that the inhaled treprostinil worked in WHO Group 3 patients.

Q. In the discussions you had with Dr. Waxman, did he ever express a belief that treprostinil would not be effective in the treatment of PH-ILD patients?

A. You mean before the study unblinding?

Q. Um-hmm.

A. Before the study unblinding, in general sense you don't know. Nobody knows whether or not -- what is the result going to turn out after the study unblinding.

738. Kevin Laliberte also testified that about his doubts concerning the success of the INCREASE study:

Q. Sure. So even through in 2015 you thought it would be challenging to move forward with the INCREASE study you thought based on the element of learning that you mentioned previously that you could design a trial where it would be successful?

A. There was no expectation that it would be successful. We knew that the study needed to be conducted and then the results of the study dictated whether it was successful or not. So it was unknown.

739. [REDACTED]

740. Dr. Peterson testified about her involvement and the involvement of Drs. Deng and Smith.

741. Dr. Smith also testified about his involvement and the involvement of Drs. Peterson and Deng in the INCREASE study.

742. Dr. Deng testified about his involvement and the involvement of Dr. Peterson and Dr. Smith in the INCREASE study.

743. Dr. Waxman did not contribute to the conception of any claim of the '327 patent, and the '327 patent correctly names Leigh Peterson, Peter Smith, and Chunqin Deng as the only inventors because only they contributed to conception.

744. Dr. Waxman studied patients with more severe PH or PH that is out of proportion with the patient's ILD. Dr. Waxman's contributions reflected in Agarwal 2015 and Faria-Urbina 2018 were not sufficiently definite and permanent to constitute a conception of improvements in exercise capacity of PH-ILD patients at the claimed dosage of the '327 patent.

745. PH-ILD patients assessed in the INCREASE trial are a patient population claimed by the '327 patent, and Tyvaso is approved for patients with PH-ILD based upon those INCREASE trial results.

746. Dr. Waxman's purported idea of treating Group 3 patients with inhaled treprostinil was at most experimental, hypothesis-generating, and based on his high level of expertise with treating Group 1 patients.

747. Dr. Waxman's purported hypothesis that inhaled treprostinil could work for all PH groups was based on perceived overlaps in the underlying diseases and was later proven incorrect

by the PERFECT study, which showed that inhaled treprostinil was harmful to Group 3 PH patients with COPD.

748. The PERFECT Study was a phase III clinical study sponsored by UTC to evaluate whether the administration of inhaled treprostinil results in improved exercise capacity in patients with PH due to COPD. The study design called for administering treprostinil with a target dosage of 72 micrograms in 12 breaths, four times daily. This study illustrated that even within Group 3 PH, a drug and mode of delivery that has been shown to benefit one disease sub-population might not benefit and could even be harmful to another sub-population of patients within the same group.

749. In view of the negative results of the PERFECT study and general industry skepticism concerning the treatment of PH-ILD with therapies approved for Group 1 PH patients, Dr. Waxman's abstract and report concerning experimental treatment of a small number of purported Group 3 PH patients with inhaled treprostinil, without placebo control, maintained prescribing practice uncertainty.

750. Dr. Waxman could not have conceived of a method of improving exercise capacity in Group 3 patients—let alone PH-ILD patients—without extensive further research or experimentation.

751. Dr. Waxman testified that the idea to try inhaled treprostinil in Group 3 PH patients was based upon what was publicly explored by others in the field—knowing inhaled treprostinil was effective for Group 1 PH patients and knowing there were potential commonalities among the five PH groups. Dr. Waxman thought that Group 3 patients with “mostly destructive lung disease [were] probably not going to respond to a pulmonary vasodilator” such as treprostinil.

752. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

753. Before INCREASE, a POSA could not have known, intended or expected that the adverse events from potential V/Q mismatch would not have outweighed the benefits of administration or would not have caused a RCT to fail. Further, a POSA would know there were other concerns outside of V/Q mismatch that needed to be explored by a RCT.

**C. Defendant's Alleged Prior Art References**

754. Any prior art references relied upon by Defendant that pre-date the priority date cannot render the Asserted Claims obvious.

**1. Saggar 2009**

755. R. Saggar, et al., Treprostinil to Reverse Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis as a Bridge to Single-Lung Transplantation, 28(9) J. HEART AND LUNG TRANSPLANT 964 (2009) ("Saggar 2009") describes a retrospective case report of a 67-year-old woman with PH-ILD in the setting of a patient with Usual Interstitial Pneumonia ("UIP") pattern fibrosis, COPD, and pulmonary hypertension treated with background mycophenolate mofetil, sildenafil, and eventually IV treprostinil using a pre/post study design.

756. Saggar 2009 did not contain any exact values for the 6MWD and brain natriuretic peptide levels.

757. The authors of Saggar 2009 conclude that the "merits of long-term prostanoid therapy need further study."

758. A POSA reading Saggar 2009 would not have had a reasonable certainty that inhaled treprostinil could improve exercise capacity in PH-ILD patients.

759. A POSA would have understood that Saggar 2009 concerned a single patient observational study with intravenous ("IV") treprostinil.

760. A POSA would have understood that the patient studied in Saggar 2009 would have been ineligible for the INCREASE study given an elevated PAWP above 15 mmHg.

761. A POSA would have been unable to determine whether the physiologic changes in the patient studied in Saggar 2009 were due to IV treprostinil or furosemide, if either, given the drugs were administered simultaneously and the data were not controlled for Hawthorne or placebo effects.

## **2. Saggar 2014**

762. Saggar 2014 is a small, unblinded, open label study with no placebo control, using intravenous or subcutaneous treprostinil. The authors of Saggar 2014 acknowledge that “[t]he absence of a placebo arm is a particularly significant limitation; therefore, our findings must be confirmed with a randomized, placebo-controlled trial.”

763. Saggar 2014 had no control treatment. Saggar 2014 was conducted at a tertiary medical center. The primary and secondary endpoints are not clearly specified.

764. The small sample size of Saggar 2014 and that all patients were selected for referral to UCLA’s tertiary site for lung transplantation evaluation indicates that the data reported may be unrepresentative of PH-ILD patients.

765. A POSA would understand that changing treprostinil’s mode of administration to inhalation instead of the intravenous or subcutaneous administration used in Saggar 2014 affects the pharmacokinetics of the drug. The authors of Saggar 2014 further cautioned readers that “the explanation proposed for the lack of significant hypoxemia with parenteral prostanoid in our PH-PF cohort remains speculative and requires further investigation.”

766. Saggar 2014 does not report a significant change in FVC as a result of treprostinil administration.

767. Saggar 2014 describes patients with advanced pulmonary hypertension.

768. The authors of Saggar 2014 caution POSAs that “[a]t this point, the routine use of PH-targeted therapy in PH-PF is not recommended and should only be cautiously considered at specialized PH centers to avoid the serious potential for worsening cardiopulmonary status in this patient population.”

769. The authors of Saggar 2014 counseled POSAs that “parenteral [(injections as opposed to inhaled)] prostanoid therapy [is] associated with worsening of ventilation-perfusion (V-Q) mismatch and subsequent hypoxemia [which] remains a major clinical concern.”

770. The authors of Saggar 2014 admit that the “[l]imitations of this study include the heterogeneity of the PF population, variable background PH-targeted therapy, and the absence of ABG testing.”

771. The authors of Saggar 2014 admit that the absence of a placebo arm is a “particularly significant limitation.”

772. The authors of Saggar 2014 counseled POSAs that the study “findings are only hypothesis generating and require confirmation in a multicentre, randomised study design.”

773. A POSA would have understood that Saggar 2014 used change scores (comparing to baseline) and these scores are subject to various biases, so they cannot be used to draw inferences about the effectiveness of the treatment. The FVC scores reported in Saggar 2014 are not statistically significant.

774. A POSA reading Saggar 2014 would not have had a reasonable certainty that inhaled treprostinil could improve exercise capacity in PH-ILD patients.

775. A POSA would have understood that Saggar 2014 concerned a small prospective, unblinded, uncontrolled study with parenteral treprostinil.

776. A POSA would have understood that the PAWP inclusion criteria for Saggar 2014



listed on the clinicaltrials.gov entry targeted a different patient population that was included in the INCREASE study.

777. A POSA would have understood that some of the patients in Saggar 2014 had combined pre- and post-capillary PH complicating ILD.

778. A POSA would have understood that Saggar 2014 does not report data for assessment of alveolar abnormalities required for acute exacerbation diagnosis by ATS criteria.

779. A POSA would have understood that a reduction in exacerbations does not necessarily follow from a reduction in dyspnea in PH-ILD patients.

780. A POSA would have understood that that FVC results reported in Saggar 2014 were not statistically significant.

781. A POSA would have understood that Prins 2017 concluded that Saggar 2014 had a sufficient degree of bias.

782. One of the authors of Saggar 2014, Dr. Rajan Saggar, has testified that he reviews publications that he is a named author of for truth and accuracy.

783. Dr. Rajan Saggar is a named, senior author on another publication titled *Pulmonary Hypertension Complicating Interstitial Lung Disease and COPD* that was published prior to Saggar 2014, in 2013, in *Seminars of Respiratory and Critical Care Medicine* (“Shino 2013”). The authors of Shino 2013 state that “[i]n general, PH-specific therapies in this setting have been poorly studied, with concern for increased shunting and/or ventilation/perfusion (V/Q) mismatch and resultant hypoxemia.” Dr. Saggar testified that it was correct and “a reasonable statement.”

784. The authors of Shino 2013 state that PH-therapies, including treprostinil, “have been well studied in Group I PAH, but data regarding their use in Group III (IPF-associated PH) ... are limited to small nonrandomized studies.” Dr. Saggar testified that IPF-associated PH is PH-

ILD and that this statement included uncontrolled studies.

785. The authors of Shino 2013 state that “[g]uidelines discourage the use of these agents due to the lack of data demonstrating the efficacy and safety concerns.” Dr. Rajan Saggar’s testimony confirms this: “pulmonary hypertension therapies approved for Group I PAH generally [we]re discouraged [for] the use of Group III PAH at that time.”

786. The authors of Shino 2013 state that “the role of medical pharmacotherapy for IPF-PH has not been well studied and remains controversial. Additional studies are required to determine if some subsets of IPF patients with PH may benefit from PH-specific therapy.” Dr. Rajan Saggar confirmed that statement applied to PH-ILD patients as IPF-PH is the most common type of PH-ILD.

787. The authors of Shino 2013 state that “PH-specific therapies have minimal proven benefit and should be used with caution. Significant PH complicating parenchymal lung disease should trigger a referral for LT.” Dr. Saggar confirmed that “LT” stood for “lung transplant.”

788. Dr. Rajan Saggar is a named author on another publication titled *Idiopathic Pulmonary Fibrosis: Epidemiology, Clinical Features, Prognosis, and Management* that was published in 2016, in *Seminars of Respiratory and Critical Care Medicine* (“Lynch 2016”). Dr. Saggar confirmed that Lynch 2016 states “[t]he impact of treating PAH in patients with IPF has not been elucidated.” Dr. Saggar also confirmed that Lynch 2016 states that “[t]he role of PAH-specific agents such as prostacyclin analogues, phosphodiesterase inhibitors, and/or ET-1 receptor antagonists is controversial,” which includes treprostinil. Dr. Saggar also confirmed that Lynch 2016 states that “[g]uidelines discouraged the use of these agents due to lack of data demonstrating efficacy, safety concerns, and expense.” Dr. Saggar also confirmed that Lynch 2016 states that “the role of medical pharmacotherapy for IPF-PAH has not been well studied and remains

controversial,” with IPF-PAH being a type of PH-ILD. Dr. Saggar confirmed that Lynch 2016 states that severe PAH is “mPAP more than 40 millimeters of mercury,” and that “most people would agree that that’s severe.” Dr. Saggar confirmed that Lynch 2016 discusses Saggar 2014 and stated that its results show “modest improvement in RV function without worsening hypoxemia.”

789. Dr. Rajan Saggar is a named author on another publication titled Pulmonary Hypertension Related to Chronic Obstructive Pulmonary Disease and Diffuse Parenchymal Lung Disease A Focus on Right Ventricular (Dys)Function that was published in 2018, in Heart Failure Clinics (“Tseng 2018”). Dr. Saggar confirmed that Tseng 2018 states that “[t]here is limited evidence supporting the use of PH-specific therapy in COPD and DPLD,” with DLPD including ILD. Dr. Saggar confirmed that Tseng 2018 did not address any FVC data from Saggar 2014, but addressed approved hemodynamic, 6MWD, and BNP without hypoxemia.

790. Dr. Rajan Saggar is a named author on another publication titled *Il Buono, Il Brutto, Il Cattivo* that was published in 2014, in Thorax, in response to criticism and commentary of Saggar 2014 (“Il Buono 2014”). Dr. Saggar agreed that Il Buono 2014’s statements reflect that he was “hoping [his] study would help set the stage to help design another study and that that study would hopefully revolutionize the management of patients with PF-PH which is a type of PH-ILD.”

### **3. The 2009 Tyvaso Label**

791. The 2009 Tyvaso Label is an FDA-approved label describing “TYVASO (treprostinil) inhalation solution” published in 2009.

792. The 2009 Tyvaso Label does not disclose any information about PH-ILD or the administration of inhaled treprostinil in PH-ILD patients. The 2009 Tyvaso Label specifically teaches that the safety and efficacy of Tyvaso has not been established in patients with significant underlying lung disease.

793. The 2009 Tyvaso label instructs patients to titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session.

794. The 2009 Tyvaso label does not indicate how to correctly calculate an appropriate dose to improve the exercise capacity of a patient with PH-ILD.

795. The 2009 Tyvaso label describes the TRIUMPH I study, which enrolled patients consuming an additional PH medication, which a POSA would understand could impact the dosage of treprostinil necessary to see a change in exercise capacity for PH-ILD patients.

796. The 2009 Tyvaso Label was considered by the Examiner during prosecution of the '327 Patent.

#### **4. Agarwal 2015**

797. Agarwal 2015 is an abstract reporting on a retrospective, single-center, single-arm, open-label chart review following 35 purportedly WHO Group 3 patients that were administered inhaled treprostinil. At least 15 patients in Agarwal 2015 did not have PH-ILD.

798. Agarwal 2015 does not disclose or calculate the dosage of treprostinil/breath.

799. The primary and secondary endpoints were not identified. There are no details as to how adverse events were tracked.

800. Agarwal 2015 combines all three classifications of patient into a single group for analysis, and it does not provide any method by which the results for any specific sub-population can be determined, and whether those sub-population results are statistically significant.

801. The small sample size of Agrwal 2015 suggests that the data reported by Agarwal 2015 cannot be representative of PH-ILD patients.

802. Agarwal 2015 does not describe the inclusion or exclusion criteria used for patients or how patients were screened for eligibility. Thus, a POSA would not have been able to ascertain whether PH-ILD patients were included in this analysis, and, if they were, what proportion of the

“restrictive” patients had PH-ILD.

803. Agarwal 2015 did not account for patients that discontinued the study, which reflects selection bias.

804. Agarwal 2015 only contains 6MWD data for 60% of patients observed. Agarwal 2015 and the March 2015 Presentation provide different 6MWD results for mixed lung disease patients.

805. Agarwal 2015 does not report a change in dyspnea or WHO function over a 6-month period.

806. Agarwal 2015 does not report change scores for 8, 12, or 16 weeks.

807. Agarwal 2015 reports 30 of the 35 followed patients reported “subjective improvement,” but Agarwal 2015 also reports that only 24 of 26 followed patients that continued therapy for 6 months reported improvement and does not reconcile this data.

808. Agarwal 2015 does not discuss the use of dual therapy in 15 patients that is reported in the March 2015 Presentation given by Dr. Waxman.

809. The March 2015 Presentation given by Dr. Waxman acknowledges that Agarwal 2015 was subject to limitations including small numbers of patients enrolled, highly selected patients in terms of lung disease, and it was not randomized.

810. The change scores (comparisons to baseline and follow-up data) in Agarwal 2015 cannot be used to draw inferences about the effectiveness of the treatment.

811. The authors of Agarwal 2015 indicate that “a prospective clinical trial is indicated.”

812. A POSA would have understood that Agarwal 2015 concerned a retrospective, uncontrolled study with inhaled treprostinil in WHO Group 3 patients.

813. Agarwal 2015 does not disclose a dry powder formulation of treprostinil.

814. The examiner of the '327 patent allowed the Asserted Claims over Agarwal 2015 after reviewing its disclosure.

815. Agarwal 2015 is identified in the specification of the '327 patent.

### **5. The 2017 INCREASE Study Description**

816. The 2017 INCREASE Study Description is a publication from ClinicalTrials.gov that describes a proposed inhaled treprostinil study to be performed by UTC to determine what the effects of inhaled treprostinil administration might be on PH-ILD patients.

817. The INCREASE study had not yet been performed at the time of the publication of 2017 INCREASE Study Description and thus the POSA would understand that the outcomes were to be determined and uncertain. The POSA would also understand that the INCREASE study was proposed because its outcomes were uncertain. Because of this uncertainty, each secondary outcome measures would also have been uncertain at the time of publication. These secondary outcome measures include change in 6MWD from baseline to week 12, change in trough 6-minute walk distance from baseline to week 15, change in plasma concentration of n-terminal pro-brain natriuretic peptide from baseline to week 16, forced expiratory volume in one second from baseline to week 16, change in forced vital capacity from baseline to week 16, change in total lung capacity from baseline to week 16, change in lung diffusion capacity from baseline to week 16, and incidence of adverse effects among participants through 16 weeks.

818. The 2017 INCREASE Study Description also proposes a dosage of approximately 6 µg per breath. The 2017 INCREASE Study Description provides for use of the inhaler four times daily, titrated up to a maximum of 12 breaths each time. However, the 2017 INCREASE Study Description does not provide any results of treprostinil administration, nor any expected results.

819. The 2017 INCREASE Study Description shows that the INCREASE trial was designed to test whether there would be a treatment effect on exercise capacity as measured by

6MWD and whether to test impact on other measures.

820. The 2017 INCREASE Study Description corresponds to Study Record Version 23 for INCREASE, i.e., the 23<sup>rd</sup> version of the study description submitted to ClinicalTrials.gov. The 2017 INCREASE Study Description was posted on ClinicalTrials.gov on February 10, 2017, and describes the proposed study to be carried out, including the basic elements of study design, the interventions to be studied, the outcome measures, and patient eligibility. Study Record Version 24, which was posted on March 3, 2017, updated and clarified the study description, secondary outcomes measures, and participant eligibility criteria. Study Record Version 85, which was posted on January 10, 2020, updated the study recruitment status from “recruiting” to “completed.” Study Record Version 88, which was posted on June 6, 2020, updated the secondary outcome measures to add “Time to Clinical Worsening.” Study results were first submitted to ClinicalTrials.gov on April 29, 2021, and were first posted on May 24, 2021. At no time prior to April 17, 2020—indeed, at no time prior to May 24, 2021—were any INCREASE study results or findings reported on ClinicalTrials.gov.

821. As of April 17, 2020, a POSA reading the 2017 INCREASE Study Description (i.e., Study Record Version 23) in April 2020 would understand it to be outdated and not reflect how INCREASE was actually performed. For example, Study Record Version 24, which superseded Study Record Version 23 on March 3, 2017 contains substantial changes to the protocol, including to the exclusion and inclusion criteria for participating patients as well as the secondary endpoints involved. Thus, a POSA would not attribute any results of the INCREASE study to the particular study design disclosed in the 2017 INCREASE Study Description, which was never performed.

## **6. Faria-Urbina 2018**

822. Faria-Urbina 2018 reports a retrospective, single-site, single-arm, open-label chart review that screened 72 patients presenting with pulmonary hypertension that were administered

inhaled treprostinil at the Pulmonary Vascular Disease Clinic at Brigham and Women's Hospital from December 2009 to November 2016. The patients were screened for  $\text{mPAP} \geq 35$  mmHg (which the authors' characterize as "severe PH") or a  $\text{mPAP} \geq 25$  mmHg associated with pulmonary vascular resistance ( $\text{PVR} \geq 4$  Woods Units).

823. Ultimately, only 22 patients were examined. Of these patients, only 9 had ILD. The study thus has a small sample size, heterogeneous patient cohort, and an unrepresentative cohort. The data reported by Faria-Urbina is likely not representative of PH-ILD patients in general.

824. The 6MWD test was administered based on the treating physician's judgment.

825. The change scores reported in Faria-Urbina 2018 cannot be used to draw inferences regarding the effectiveness of the treatment.

826. Patients in Faria-Urbina 2018 were on dual therapies, limiting the ability to discern effects attributable to treprostinil.

827. Conclusions about efficacy in improving 6MWD cannot be appropriately drawn about the entirety of the PH-ILD patient population based on a sample size of 3 patients.

828. A POSA would recognize that there was a directional trend toward greater desaturation on both 6MWT and 3-minute step testing assessment.

829. The authors of Faria-Urbina indicate that the chart review results should be interpreted carefully in view of the small sample size and the heterogeneity of the population (COPD, ILD, and Combined Pulmonary Fibrosis and Emphysema ("CPFE")).

830. The authors of Faria-Urbina also note that their findings are limited by "the intrinsically subjective nature of FC assessment, and the lack of a control group."

831. Faria-Urbina 2018 does not report change scores for 8 weeks and may not report change scores reflecting 12 or 16 weeks.



832. Follow-up timing in Faria-Urbina 2018 was at the discretion of the treating physician and was not uniform across patients in the study.

833. A POSA would have understood that Faria-Urbina 2018 concerned a retrospective, unblinded, uncontrolled study with inhaled treprostinil.

834. A POSA would have understood from the overlap in authors and experimental design of Agarwal 2015 and Faria-Urbina 2018 that there may have been overlap in the reported patient population.

835. Faria-Urbina 2018 is an uncontrolled “retrospective” report that describes “data from 22 patients with PH associated with lung disease treated with inhaled treprostinil (iTre) and followed up clinically for at least 3 months.”

836. In general, a POSA would not rely on an uncontrolled, retrospective report like Faria-Urbina 2018 to determine the effect of inhaled treprostinil because it suffers from a number of defects, including a lack of control over the analyzed population, sampling bias, and a small heterogenous patient population.

837. Faria-Urbina 2018’s study began with 61 patients with PH and lung disease, but only analyzed 22 of those patients.

838. Of the 22 patients analyzed in Faria-Urbina 2018, 14 were reported as having ILD.

839. The “[t]herapies related to the underlying lung disease were continued throughout the observation period” for the patients analyzed in Faria-Urbina 2018.

840. The follow-up analyses studied in Faria-Urbina 2018 were taken at > 3 months.

841. Faria-Urbina 2018 was considered by the patent examiner during the prosecution of the application that would become the ’327 Patent.

842. A POSA would also have recognized that Agarwal 2015 and Faria-Urbina 2018

came out of the same research group and may have had had an overlapping patient population.

843. The authors of Faria-Urbina 2018 state that “[t]he potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in larger prospective studies.” Further, the authors state that “[u]ntil then, [inhaled treprostinil]’s use in Group 3 PH should be cautiously evaluated in specialized PH Centers, after an individualized assessment and risk-benefit consideration.”

## **7. February 2020 Press Release**

844. United Therapeutics released a press release on February 24, 2020 (Press Release, United Therapeutics Announces INCREASE Study of Tyvaso® Meets Primary and All Secondary Endpoints (Feb. 24, 2020)) (“February 2020 Press Release”), describing the successful completion of its INCREASE trial based on a preliminary analysis.

845. The February 2020 Press Release is not prior art to the ’327 Patent.

846. The February 2020 Press Release was published within 1 year of the April 17, 2020 filing date of the ’810 Provisional Application, to which the ’327 patent properly claims priority.

847. The February 2020 Press Release contains information disclosed directly from one or more named inventors of the ’327 patent. The February 2020 Press Release contains a direct quotation from inventor Leigh Peterson.

848. The February 2020 Press Release contains information disclosed indirectly from one or more named inventors of the ’327 patent. The February 2020 Press Release contains results and data from the INCREASE trial, which was conducted and supervised by the named inventors of the ’327 patent. For example, named inventor Chunquin Deng was responsible for compiling and analyzing the data from the INCREASE trial.

849. Because it is a disclosure made by the joint inventors of the ’327 patent or by another who obtained the subject matter disclosed directly or indirectly from the joint inventors 1

year or less prior to the effective filing date of the '327 patent, the February 2020 Press Release meets all the requirements of the exception listed under 35 U.S.C. § 102(b)(1)(A). The February 2020 Press Release therefore does not qualify as prior art to the '327 patent under 35 U.S.C. § 102(a)(1).

850. The February 2020 Press Release is a UTC press release giving the top-line results of the INCREASE study, which analyzed the effects of inhaled treprostinil administration to patients with PH-ILD.

851. A POSA would not consider a press release a viable source of information for making medical decisions, and therefore would not use it to practice a method of treprostinil administration.

852. The February 2020 Press Release does not contain any of the analysis performed as part of the INCREASE study. The 2020 Press Release does not provide the underlying data necessary to form an intent or expectation to solve the problem identified by the '327 patent nor confirmation that the FDA has reviewed and approved the underlying data and PH-ILD indication. The 2020 Press Release states that the results have not yet been submitted to the FDA to support an efficacy supplement and revised labeling, and that "Detailed study results will be made available through scientific disclosure at upcoming medical conferences and in peer-reviewed publications."

853. The February 2020 Press Release does not disclose any FVC data from the INCREASE trial.

854. The February 2020 Press Release does not disclose the use of a dry powder inhaler to deliver inhaled treprostinil to PH-ILD patients.

855. The February 2020 Press Release explained that this was the first clinical trial to

demonstrate a benefit for PH-ILD patients and reported improvements in 6MWD after 16 weeks of treatment across several sub-groups—with 6MWD being the primary efficacy endpoint. The February 2020 Press Release also disclosed a series of secondary endpoints, such as reduction in NT-proBNP concentration, time to first clinical worsening event, change in peak 6MWD at week 12, and change in trough 6MWD at week 15.

## **8. '793 Patent**

856. U.S. Patent No. 10,716,793 (“’793 patent”) is titled “Treprostinil Administration By Inhalation” and was issued by the Patent and Trademark Office on July 21, 2020. The ’793 patent is a patent directed to the use of treprostinil to improve the hemodynamics of patients suffering from pulmonary hypertension. It does not disclose any methods directed to improving exercise capacity in patients with PH-ILD. It further does not disclose any improvement in any patient-centered outcome.

857. The ’793 patent is not prior art to the ’327 patent.

858. The ’793 patent issued, and thus became publicly available, after the April 17, 2020 filing date of the ’810 Provisional Application, to which the ’327 patent claims properly priority. Thus, the ’793 patent does not qualify as prior art to the ’327 patent under 35 U.S.C. § 102(a)(1).

859. As of April 17, 2020, both the ’793 patent and the ’327 patent were assigned to Plaintiff, and were thus commonly owned by Plaintiff. Thus, the ’793 patent does not qualify as prior art to the ’327 patent under 35 U.S.C. § 102(a)(2) because it meets all the requirements of the exception listed under 35 U.S.C. § 102(b)(2)(C).

860. Example 1 of the ’793 patent describes a study involving 13 patients with idiopathic PAH, other forms of PAH, CTEPH, and pulmonary fibrosis where the analysis was done on a patient group basis not a patient by patient basis. Example 1 does not report any hemodynamic or gas exchange data that is specific to the subgroup of patients with a pulmonary fibrosis disease

etiology.

861. Example 2 of the '793 patent describes three different studies, none of which described the results of treprostinil administration to patients with PH-ILD. Example 2 does not make any specific reference to the improvement of any hemodynamic parameter on a patient-specific basis.

862. The '793 patent does not describe the appropriate dosage of a dry-powder formulation of treprostinil for any indication.

863. A POSA would not have understood that pulmonary fibrosis as described in the '793 patent is a form of PH-ILD, and that PH-ILD patients were treated in the '793 patent examples.

864. A POSA would have known, both on the filing date of the '793 patent and the '327 patent, that lowering PAP in a patient with Group 2 pulmonary hypertension could potentially be harmful to the patient.

865. A court has previously construed the “therapeutically effective single event dose” of the '793 patent to refer only to the dose required to have a hemodynamic impact.

866. A POSA reading the '793 patent would not have had a reasonable certainty that inhaled treprostinil could improve exercise capacity in PH-ILD patients.

867. A POSA would have understood that the '793 patent concerned the observation of hemodynamic parameters over a two-hour period following a single administration event.

868. A POSA reading the '793 patent would have understood that the reported data is aggregated for all disease types rather than stratified to the pulmonary fibrosis group, which only included 4 patients.

869. A POSA reading the '793 patent would have understood that in the one instance

where the pulmonary fibrosis patients made up the majority of the aggregate data, there was a significant decrease in arterial oxygen after receiving a single dose of treprostinil, indicating a potential safety concern.

870. A POSA reading Example 1 and Table 2 of the '793 patent would have understood that it did not concern chronic administration of treprostinil, exercise testing, statistical analysis, or a robust patient population or placebo group.

871. A POSA reading Example 2 and Table 3 of the '793 patent would have understood that it did not concern chronic administration of treprostinil, exercise testing, or subgroup analysis and only observe hemodynamic data for up to 180 minutes following a single administration event.

872. The '793 patent does not cover a method of treating PH-ILD patients with inhaled treprostinil and improving their exercise capacity.

873. The Court has previously found that “[b]ased on the record before [the Court], the '793 patent does not teach administering inhaled treprostinil to specifically improve exercise capacity, nor does the disclosed data discuss improved exercise capacity.”

874. The '793 patent does not disclose the dosing regimen that is claimed by the methods of the '327 patent.

875. The '793 patent does not disclose anything that would allow an individual to perform the claimed methods with the intentional purpose or expectation of improving exercise capacity, as required by claim 1 of the '327 patent.

876. Examples 1 and 2 of the '793 patent do not disclose patients with PH-ILD. Examples 1 and 2 do not provide a POSA with sufficient information to know whether any of the alleged PH-ILD patients received treprostinil at the doses required by any claim of the '327 patent or at all.

877. The hemodynamics described in the '793 are not correlated with improved exercise capacity. This Court has previously held that the therapeutic effect claimed in the '793 patent was directed to hemodynamic improvements.

878. Shaun Snader testified as follows regarding a letter submitted by UTC to the FDA on February 12, 2024 concerning the '793 patent:

Q. Were you involved in the preparation of this letter?

A. Yes.

Q. What was the nature of your involvement in the preparation of this letter?

MR. JACKSON: I'm going to instruct the witness not to answer on the grounds that that involves the attorney-client privilege and attorney work product doctrine.

BY MR. DAVIES: Q. You're going to follow your attorney's instruction?

A. Yes.

## **9. Parikh 2016**

879. Parikh 2016 reports a retrospective, single-center, single-arm, open-label chart review of 80 patients that was conducted to evaluate the safety and tolerability of high-dose inhaled treprostinil.

880. The primary endpoints of Parikh 2016 were safety and tolerability.

881. Two-thirds or more of the subjects studied in Parikh 2016 were on at least one additional hypertension therapy.

882. In Parikh 2016, only 78 of the 80 followed patients made it to 12 breaths four times daily, and 20 of those 78 patients discontinued inhaled treprostinil during follow-up. Further, only 49 patients had data for follow-up visit 1 and only 39 patients continued until follow-up visit 2.

883. The authors of Parikh 2016 caution that the study "was limited by the retrospective

study design and only included patients thought to be good candidates for higher dose iTRE. Because this was an observational study in clinical practice it also suffers from follow-up loss.” Further, the authors state that there was “insufficient follow-up data to analyze efficacy endpoints.”

884. Parikh 2016 reports change scores, which cannot be used in statistical analyses to draw inferences about the effectiveness of the treatment.

885. The follow-up visits reported in Parikh 2016 occurred at varying timepoints.

886. Only 6 patients in Parikh 2016 reportedly have Group 3 ILD/fibrosis and only 6 have Group 3 mixed pattern. The small sample size used in Parikh 2016 means that the data from Parikh 2016 is unrepresentative of PH-ILD patients.

887. The data from patients examined in Parikh 2016 were aggregated and it is not possible to determine the effect of treprostinil on the 6 PH-ILD patients.

888. A POSA reading Parikh 2016 would not have had a reasonable certainty that inhaled treprostinil could improve exercise capacity in PH-ILD patients.

889. A POSA would have understood that Parikh 2016 concerned a retrospective, unblinded, uncontrolled study with inhaled treprostinil.

890. A POSA would have understood that of the 80 patients enrolled in Parikh 2016, 6 were identified as having “interstitial lung disease/fibrosis;” however Parikh 2016 fails to identify how the diagnosis of these patients were adjudicated.

891. A POSA would have understood that Parikh 2016 only reports data on a population level and does not report data for any PH-ILD subgroups.

892. A POSA reading Parikh 2016 would have understood that that the heterogeneity in follow-up interval and high dropout rate obscures the ability to identify any meaningful biological trends.



**10. Wade '200**

893. Wade '200 was published on April 18, 2013, and is entitled "Treprostinil treatment for interstitial lung disease and asthma." Wade '200 is an abandoned patent application. Wade '200 discusses the use of treprostinil in connection with interstitial lung disease by treating a condition associated with interstitial lung disease.

894. Wade '200 does not disclose any results of administering treprostinil to humans. Wade '200 does not disclose the results of its proposed dosing schedules. Wade '200 does not disclose any changes in 6MWD in response to treprostinil administration.

**11. Additional References**

a) [REDACTED]

895. [REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

**b) Waxman 2015 Presentation**

898. A presentation entitled “Tyvaso in WHO Group 3” and containing the date March 9, 2015 (the “Waxman 2015 Presentation”) indicates that 15 patients received dual therapy for at least a portion of the study, and “tolerated the addition of a systemic pulmonary vasodilator (PDE5i).”

899. The Waxman 2015 Presentation described that the study was subjected to several limitations, including “[s]mall numbers,” “[h]ighly selected in terms of lung disease,” and “[n]ot a randomized trial.”

900. The Waxman 2015 Presentation notes that the participants were “newly diagnosed patients ... with severe symptoms” and that the study was “[h]ighly selected in terms of lung disease,” which suggests that the participants likely are not representative of WHO Group 3 PH patients as a whole.

**c) 2017 Waxman Presentation**

901. Dr. Waxman gave a presentation at the 12<sup>th</sup> John Vane Memorial Symposium (the “2017 Waxman Presentation”).

902. Dr. Waxman stated that his studies “provide some support ... that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered.”

903. A POSA would understand that Dr. Waxman’s statements suggest a hypothesis to be tested, not a reasonable expectation of success.

904. Dr. Waxman was presenting the data reported in Faria-Urbina 2018. All of the limitations and biases in Section V.C.6 apply to Dr. Waxman’s presentation..

**d) 2017 INCREASE Study Protocol**

905. The 2017 INCREASE Study Protocol cited by Defendant corresponds to the 2017 INCREASE Study Description, i.e., Study Record Version 23 for INCREASE. As discussed above, the clinical trial design described in Study Record Version 23 is different from what was actually performed during the INCREASE trial. A POSA would therefore view the 2017 INCREASE Study Protocol as outdated and irrelevant.

906. The INCREASE Study Protocol included the FVC and exacerbations of underlying lung disease endpoints as safety endpoints, which raised significant concerns about patient health and uncertainty going into the INCREASE study.

**e) 2018 Science Day Presentation**

907. Dr. Waxman gave a presentation in 2018 at UTC's Science Day (the "2018 Science Day Presentation").

908. Dr. Waxman was presenting the data reported in Faria-Urbina 2018. All of the limitations and biases in Section V.C.6 apply to Dr. Waxman's presentation.

909. At the 2018 Science Day Presentation, Dr. Waxman stated:

So we felt that this pilot study, again, retrospective, gave us preliminary evidence that there was good reason to consider treating patients with pre-capillary pulmonary hypertension in the setting of advanced lung disease, and this led to discussions with United Therapeutics and development of 2 clinical trials, the INCREASE study and the PERFECT study.

910. A POSA would understand Dr. Waxman's statements to suggest that Faria-Urbina 2019 was not immediately persuasive to UTC.

911. The online publication date of the 2018 Science Day presentation by Dr. Waxman is not established.

**f) 2018 UTC Earnings Call**

912. The Earnings Call for UTC for the First Quarter of 2018 (the “2018 UTC Earnings Call”) is not a document upon which a POSA would have relied on. The 2018 UTC Earnings Call began with a disclaimer explaining that “[t]oday’s remarks may discuss the progress and results of clinical trials or other developments with respect to our products. These remarks are intended to solely educate investors and are not intended to serve as the basis for medical decision making or to suggest that the products are safe and effective for any unapproved or investigational uses. Full prescribing information for the products is available on our website.”

913. The 2018 UTC Earnings Call does not specify that physicians were using treprostinil specifically for PH-ILD patients. Dr. Rothblatt’s remarks are directed to Group 3 PH broadly, including both PH-ILD and PH-COPD, which Dr. Rothblatt specifies “are 2 distinct populations.”

914. The 2018 UTC Earnings Call provides a possibility of a placebo effect, which was later confirmed when the INCREASE study reported significant increases in 6MWD in some patients in the placebo group. A POSA would have been aware of the possibility of a placebo effect and would have required additional data before believing that treprostinil had any clinical benefit, including an exercise capacity benefit, for patients with PH-ILD.

915. Dr. Rothblatt’s statements in the 2018 UTC Earnings Call refer to the use of inhaled treprostinil to treat WHO Group 3 PH *generally*, not only or just PH-ILD patients. Dr. Rothblatt explained that only some Group 3 PH patients saw any benefit. A POSA would not make a clinical treatment decision based on a company’s earnings call to investors.

916. Based on Dr. Rothblatt’s statements in the 2018 UTC Earnings Call and by reading the 2018 UTC Earnings Call transcript, the POSA would not be motivated to combine references because the POSA would not even know what indication the combination would be successful for.

This problem was further exacerbated by a series of failed studies that occurred after the 2018 UTC Earnings Call and would have led the POSA away from any motivation to combine references to successfully administer treprostinil for PH-ILD.

917. Dr. Channick has never suggested that the POSA would either look into the 2018 UTC Earnings Call as prior art or as a motivation to combine because Dr. Channick has only opined that it *confirms* his opinion that the POSA would expect to succeed based on other documents.

918. Dr. Channick testified that it was not his ordinary practice to review corporate earning calls. Dr. Channick also testified that he learned of the 2018 UTC Earnings Call from counsel and would never make a prescribing decision based on the contents of an earnings call.

**D. The '327 Patent is Not Anticipated**

**1. The February 2020 Press Release Does Not Anticipate Claims 1-4, 6, 8, 11, and 15-19 of the '327 Patent**

919. The February 2020 Press Release did not describe the method associated with treprostinil administration to the study population. It only explained that the treatment used was “Tyvaso(r) (treprostinil) Inhalation Solution,” and did not describe the dosages used, any upward or downward titration of that dosage over time, or any other aspects of the INCREASE trial design or results.

920. The February 2020 Press Release also noted that the results were forthcoming, but not yet publicly available.

921. The February 2020 Press Release does not contain any data from the INCREASE study.

922. The February 2020 Press Release does not describe the dosage of inhaled treprostinil given to patients in the INCREASE study.

923. The February 2020 Press Release does not describe the effect of treprostinil administration after 8 or 12 weeks of administering.

924. The INCREASE Trial data, analysis, and complete results were published in January 2021, after the February 2020 Press Release.

925. The February 2020 Press Release does not alone, or in combination with Liquidia's other asserted prior art, anticipate or render obvious any claims of the '327 Patent.

**2. Faria-Urbina 2018 Does Not Anticipate Any Claim of the '327 Patent**

926. A POSA reading Faria-Urbina 2018 would not have had a reasonable certainty that inhaled treprostinil could improve exercise capacity in PH-ILD patients.

927. A POSA reading Faria-Urbina 2018 would have understood that there was not a statistically significant increase in 6MWD for the patients adjudicated as having PH-ILD.

928. A POSA reading Faria-Urbina 2018 would have understood there to be a potential safety concern in using inhaled treprostinil to treat PH-ILD patients based on the directional trend of greater desaturation during the 6MWT and 3-minute step test.

929. The 22 patients analyzed in Faria-Urbina 2018 consisted of both COPD and ILD patients, and thus a POSA cannot determine if any results drawn from that population could be attributed to the COPD or ILD patients.

930. Faria-Urbina 2018 showed no significant improvement in functional class for patients with PH-ILD.

931. The 6MWD calculation for the PH-ILD subgroup analyzed in the Faria-Urbina 2018 supplemental document showed no significant increase in 6MWD.

932. The 6MWD calculation for the CPFE subgroup analyzed in the Faria-Urbina 2018 supplemental document was based on only three patients.

933. A POSA would not be able to determine the change in 6MWD at 8, 12, or 16 weeks

based on a measurement taken at > 3 months.

934. Faria-Urbina 2018 does not contain sufficient information to inform a POSA whether inhaled treprostinil would be effective for any particular purpose, including to increase the exercise capacity of a patient with PH-ILD or decrease exacerbations. Thus, it explains that “cautious[] evalua[tion] is required” on an “individualized” basis.

935. Due to inter-patient variability, a PH-ILD patient administered treprostinil will not necessarily experience any particular effect as a result of the administration.

936. There are “multiple steps between” Faria-Urbina 2018 and INCREASE thus, the results of one cannot be attributed to the other.

937. Faria-Urbina 2018 does not alone, or in combination with Liquidia’s other asserted prior art, anticipate (inherently or otherwise) or render obvious any claims of the ’327 Patent.

**3. The 2017 INCREASE Study Description Does Not Inherently Anticipate Asserted Claims 1-11 and 15-19 of the ’327 Patent**

938. By its very nature, the 2017 INCREASE Study Description contains no information describing the results of treprostinil administration to any person. Nor would a POSA look to the 2017 INCREASE Study Description for any information regarding an expected result of treprostinil administration.

939. No study has ever been performed as described in the 2017 INCREASE Study Description, and as such the results of performing a study as described in the 2017 INCREASE Study Description are unknown.

**4. The 2017 INCREASE Study Description does not alone, or in combination with Liquidia’s other asserted prior art, anticipate or render obvious any claims of the ’327 Patent. (Anticipated testimony of Dr. Nathan.) The 2009 Tyvaso Label Does Not Inherently Anticipate Claims 1–11 and 15–19 of the ’327 Patent**

940. The 2009 Tyvaso Label does not disclose any information about PH-ILD.

941. The 2009 Tyvaso Label does not disclose any information regarding the effects of treprostinil administration to a patient with PH-ILD.

942. The 2009 Tyvaso Label does not disclose any information derived from patients with PH-ILD.

943. Since the 2009 Tyvaso Label only describes “Tyvaso” as “indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance” a person following the instructions of the 2009 Tyvaso label would not administer it to a patient with PH-ILD.

944. The 2009 Tyvaso Label does not alone, or in combination with Liquidia’s other asserted prior art, anticipate or render obvious any claims of the ’327 Patent. Agarwal 2015 Does Not Inherently Anticipate Claims 1-3, 6, 11 and 15-19 of the ’327 Patent

945. A POSA reading Agarwal 2015 would not have had a reasonable certainty that inhaled treprostinil could improve exercise capacity in PH-ILD patients.

946. A POSA reading Agarwal 2015 would have been unable to determine whether PH-ILD patients were included in the study based on the absence of inclusion/exclusion criteria or other baseline characteristics required to diagnose ILD per ATS criteria.

947. The patients analyzed in Agarwal 2015 consisted of COPD, CFPE, and ILD patients, and thus a POSA cannot determine if any results drawn from that population could be attributed to the ILD patients.

948. Agarwal 2015 does not disclose the dosage/breath of treprostinil administered.

949. Agarwal 2015 does not alone, or in combination with Liquidia’s other asserted prior art, anticipate (inherently or otherwise) or render obvious any claims of the ’327 Patent.



**5. Dr. Nathan's Reliance on the ASCENT Study Does Not Support that the Asserted Claims are Inherently Anticipated**

950. Dr. Nathan's reliance on the ASCENT protocol to demonstrate infringement by the ASCENT study does not support that the Asserted Claim are invalid under inherent anticipation. Further, that the INCREASE results establish infringement of some of the Asserted Claims because the study results are attributable to the results that will be obtained in PH-ILD patients following administration of Yutrepia does not support the invalidity of the '327 patent as anticipated or obvious. With respect to infringement, Liquidia's protocol for its ASCENT study largely mimics the Yutrepia label, which copies the same from the Tyvaso label and the INCREASE study. Moreover, Liquidia sought approval to treat PH-ILD with Yutrepia based on (1) efficacy and safety data for Tyvaso collected in INCREASE and (2) comparative PK data showing that Yutrepia delivers an equivalent amount of treprostinil as compared to Tyvaso. Liquidia's CMO, Rajeev Saggar also testified that Yutrepia will perform as well or better than Tyvaso in the same patient population that was examined in the INCREASE study. Therefore, it is more likely than not that patients administered Yutrepia once marketed and/or as part of the ASCENT study—consistent with the ASCENT protocol—will experience the same benefits observed in the INCREASE study with respect to exercise capacity, 6MWD, NT-proBNP, acute exacerbations, clinical worsening, and FVC. By contrast, with respect to inherent anticipation, Liquidia has not established that every patient administered inhaled treprostinil in connection with any of Liquidia's asserted purported art (Faria-Urbina 2018; 2009 Tyvaso Label; 2017 INCREASE study description; Agarwal 2015) experienced the benefits required by the asserted claims with respect to exercise capacity, 6MWD, NT-proBNP, acute exacerbations, clinical worsening, and/or FVC—much less that a POSA would have understood or expected them to have as of the '327 patent's priority date. And Liquidia has further not established that any patients administered

inhaled treprostinil in connection with any of Liquidia's purported art would be considered by a POSA to be patients having PH-ILD consistent with the accepted definition of PH-ILD as of the '327 patent's 2020 priority date. As such, administration of inhaled treprostinil would not necessarily and inevitably practice these result-based claim limitations if administered prior to April 2020 and the claims are not invalid under the clear and convincing evidence standard applicable to invalidity.

**6. Prior Public Use**

**a) Physicians Did Not Use Inhaled Treprostinil to Improve Exercise Capacity in PH-ILD Patients Before April 2019**

951. Dr. Hill (Liquidia's expert) assessed prior use and prior sale using April 17, 2019 as the "relevant critical date." For this reason, Dr. Nathan (UTC's expert) also assessed prior use and prior sale using this same April 17, 2019 date as the "relevant critical date." Dr. Nathan's rebuttal opinions are equally applicable if the "relevant critical date" is set at April 17, 2020.

952. The Asserted Claims are not invalid due to purported prior public use. Inhaled treprostinil was not widely or publicly used to improve exercise capacity in PH-ILD patients before April 17, 2019. To be sure, healthcare providers including, but not limited to, Dr. Nathan, Dr. Hill, Dr. Waxman, Dr. Rajan Saggar, Dr. Rajeev Saggar, Dr. Tapson, Dr. Channick, and Dr. Parikh, neither publicly used Tyvaso in PH-ILD patients nor publicly used Tyvaso to improve exercise capacity in PH-ILD patients prior to April 2019.

**(1) Dr. Nathan Did Not Publicly Use Tyvaso Off-Label to Improve Exercise Capacity in PH-ILD Patients**

953. Before April 2019, inhaled treprostinil was not used for the purpose of improving exercise capacity in patients with PH-ILD. Healthcare providers in the United States did not publicly use Tyvaso off-label to improve exercise capacity in PH-ILD patients before April 17, 2019.

954. Dr. Steven D. Nathan did not publicly use Tyvaso off-label with the intended purpose or expectation of improving exercise capacity in PH-ILD patients prior to April 2019. Before April 2019, Dr. Nathan only prescribed PAH drugs to his patients if PAH was an appropriate diagnosis. Prior to April 2019, sildenafil was his go-to drug for this purpose.

955. Dr. Nathan testified that he had doubts concerning whether INCREASE would be successful, in part, based on his involvement in the failed RISE-IIP study:

Q. ... Do you recall sitting here today any belief by the steering committee members that the study would not be successful? ...

[A.] Yes. I had my doubts that it would be successful for sure. ...

[Q.] [W]hy did you have doubts regarding the success of the study?

A. Because it had been no prior randomized controlled study in PH-ILD demonstrating success, and personally I had just come off being the chair of the steering committee of the RISE IIP study, which was riociguat for the same indication, PH-ILD, and not only was that a negative study, but it was a harmful study.”

956. He testified that he first became optimistic INCREASE would work (to improve exercise capacity in PH-ILD patients) when the results of INCREASE were made known to him (objections omitted):

Q. So when during the development of the INCREASE study did you become optimistic that it would succeed?

THE WITNESS: When I heard the Results.

Q. So until you heard the results of the INCREASE study, you were not optimistic that the study would succeed?

THE WITNESS: I had my doubts.

Q. And when did you first hear the results of the INCREASE study?

THE WITNESS: It was sometime towards the end of February of 2020.

957. Dr. Nathan also testified that he does not recall ever prescribing inhaled treprostinil to improve exercise capacity in PH-ILD patients before seeing the results of INCREASE.

(2) Dr. Waxman Did Not Publicly Use Tyvaso Off-Label to Improve Exercise Capacity in PH-ILD Patients

958. Dr. Aaron Waxman did not publicly use Tyvaso off-label with the intended purpose or expectation of improving exercise capacity in PH-ILD patients prior to April 17, 2019.

959. The World Symposium guidelines in place as of the priority date stated that “moderate-to-severe PH” is one criteria favoring a diagnosis of Group 1 PAH.

960. Dr. Waxman’s testimony does not establish that he administered inhaled treprostinil to PH-ILD patients as the disease was understood by the POSA and defined in World Symposium guidelines as of the priority date. Indeed, his testimony does not establish that he administered inhaled treprostinil to patients whose PH was “associated with” their ILD or “due to” their lung disease.

961. Dr. Waxman testified that he administered treprostinil to patients with PH “out of proportion to any other underlying disease.” He further testified that that his retrospective studies focused on patients with PH “out of proportion to any other underlying disease.” Dr. Waxman testified that the patients he was treating were probably a “more advanced, sicker group of patients.” He treated out of proportion PH patients who likely would not have been categorized as PH-ILD patients under the 2019 World Symposium guidelines.

962. Dr. Waxman also testified that he did not know whether his hypothesis that the administration of inhaled treprostinil to PH-ILD patients would be safe and effective until the INCREASE results were made known to him:

Q. What do you remember about the day when you learned the results of the INCREASE trial?

A. When you get the call on a clinical trial, it’s kind of nail-biting

because you don't know if you were right or wrong, and I was overjoyed to hear we were, our hypothesis was right.

Q. And immediately before learning whether your hypothesis was right or wrong, how did you feel?

A. I was petrified.

Q. And why were you petrified?

A. I hate being wrong and it was a huge investment on UT's part to do the clinical trial, and also just the fact that I was convinced all these patients were doing well on a placebo-controlled trial and if it was all placebo effect, it wouldn't be a good thing.

963. Dr. Waxman is the senior author on the Agarwal 2015 and Faria-Urbina 2018 reports. The patients included in Agarwal 2015 and Faria-Urbina 2018 had disproportionately severe PH, out-of-proportion to their underlying lung disease. Patients included in Agarwal 2015 were required to have a mPAP  $\geq 35$  mmHg and a PVR  $\geq 4$  WU. Patients included in Faria-Urbina 2018 were required to have a mPAP  $\geq 35$  mmHg or an mPAP  $\geq 25$  mmHg with a PVR  $\geq 4$ WU. Faria-Urbina 2018 acknowledges that 73% of the included patients had severe PH. The Agarwal 2015 and Faria-Urbina 2018 reports specifically targeted WHO Group 3 patients that suffered from PH out of proportion to their underlying lung disease.

964. Agarwal 2015 and Faria-Urbina 2018 do not show that any of the included patients (who had ILD) were PH-ILD patients as the disease was understood by the POSA and defined in World Symposium guidelines as of April 2019. In fact, prior to April 2019, because Dr. Waxman anticipated that WHO Group 3 patients with primarily destructive lung disease would not respond to treprostinil, he leveraged hemodynamic data to identify patients with pulmonary remodeling and severe PH consistent with Group 1 PAH to "figure out who should and who shouldn't be treated." These reports do not establish that the included patients' PH was "associated with" their ILD or "due to" their lung disease.

965. The individual hemodynamic data provided in the Faria-Urbina 2018 supplemental materials for two included ILD patients are reminiscent of patients with out-of-proportion PH and who would likely be classified as having a PAH-phenotype.

966. At the 12<sup>th</sup> Annual John Vane Memorial Symposium, Dr. Waxman, discussing the Faria-Urbina 2018 report, stating:

We didn't change their pulmonary function. And I think one thing we've told all of these patients is that, "You really got two bad problems here, we're not going to fix the lung problem at all." They're going to be stuck with that, so we don't expect them to do as well as patients with just vascular disease.

(3) Dr. Tapson Did Not Publicly Use Tyvaso Off-Label to Improve Exercise Capacity in PH-ILD Patients

967. Dr. Victor Tapson did not publicly use Tyvaso off-label with the intended purpose or expectation of improving exercise capacity in PH-ILD patients prior to April 17, 2019.

968. Dr. Tapson likely only administered inhaled treprostinil to ILD patients with severe PH out of proportion with their underlying lung disease, which would likely have been Group 1 PAH patients and not PH-ILD patients with PH "due to" their lung disease as understood by a POSA and according to the 2019 World Symposium guidelines, in which "moderate-to-severe PH" is one criterion favoring Group 1 PAH.

969. Dr. Tapson testified that he treated these severely ill patients because he had no other options for treatment:

Q. You continued to use Tyvaso® in patients with PH-ILD, correct?

A. Well, "continue" makes it sound like I did it a lot. Maybe that's the way I'm interpreting it. I did do it more; again, if someone's option is death or a lung transplant, and this seems to make intuitive sense, we try to do it. But we did long for more data and we finally get it [in the INCREASE results].

970. He further testified that he carefully selected out of proportion patients from the

small number of patients with disproportionately severe PH because there was little data available and it was unclear whether the administration of treprostinil to patients with out of proportion PH to their ILD would be beneficial or even harmful.

971. [REDACTED]

972. [REDACTED]

973. Dr. Tapson also testified that he did not know that inhaled treprostinil would work to improve exercise capacity in PH-ILD patients until he received the INCREASE results. He also more generally testified that:

[W]ithout a randomized trial, you can't know something. Sometimes preliminary data looks really positive. And a randomized does not pan out, and it's the opposite. We've seen that before. So to answer your question, we didn't know if it would be ideal ahead of time. Once we had the INCREASE study, we felt like it was a good probably the best option for this disease.

(4) Dr. Rajeev Saggar Did Not Publicly Use Tyvaso Off-Label to Improve Exercise Capacity in PH-ILD Patients

974. Dr. Rajeev Saggar did not publicly use Tyvaso off-label with the intended purpose or expectation of improving exercise capacity in PH-ILD patients prior to April 17, 2019.

975. DrDsDr. Rajeev Saggar likely only treated patients with PH out of proportion with their underlying lung disease using subcutaneous or intravenous—not inhaled—treprostinil. These patients would likely have been Group 1 PAH patients and not PH-ILD patients with PH “due to” their lung disease as understood by a POSA and according to the 2019 World Symposium guidelines, in which “moderate-to-severe PH” is one criterion favoring Group 1 PAH.

976. Pre-April 2019 UTC emails do not demonstrate that claim 1 (or any of the Asserted Claims) were in public use before April 2019. For example, a June 2010 email exchange between Dr. Rajeev Saggar and UTC's CEO, Martine Rothblatt, indicates that Dr Rajeev Saggar was interested in the use of subcutaneous and intravenous treprostinil for PH-ILD, not inhaled treprostinil. Further, this email does not show that UTC or anyone else would have expected inhaled treprostinil to improve exercise capacity in PH-ILD patients.

Dear Martine,

I appreciate the opportunity to discuss the application of **SQ** treprostinil in the setting of ILD. We are BIG advocates of parenteral therapy and our research is very prostacyclin centric. UCLA is one of the largest IPF/Scleroderma/Heart-Lung Transplant centers in the world. We have invited UT one year ago to visit our center and several phase IV studies have emerged.

I would like to invite you back to UCLA and spend 1/2 day with our team and to collaborate about the use of SQ/IV TRE in the setting of ILD-PAH, scleroderma-ILD-PH and in the perioperative **transplant setting**. We have unique data that also looks at the disease process from the human tissue level. In fact, we have the largest database available (even larger than the NIH).

Most importantly, there is a new group of young investigators that think "outside of the box." As you know, it takes risky moves to advance the science. I truly [sic] believe our data is impressive and warrants further investigations. Finally, I want to acknowledge UT for the unilateral support of my ideas, concepts and my career. There is no doubt that UT's products are the key to succeed in treating ILD-PH.

With Regards,

Rajeev Saggar

977. The only PH-ILD study published by Dr. Rajeev Saggar between 2010 and April 2019, concerning ILD and treprostinil was the Saggar 2014 report. Saggar 2014 involved the administration of intravenous or subcutaneous treprostinil to pulmonary fibrosis patients with advanced PH. Indeed, the report specifically targeted pulmonary fibrosis patients with "advanced



PH,” characterized by “significant altered right heart hemodynamics and right ventricular (RV) dysfunction.” The report acknowledged that “an advanced PH phenotype in the context of chronic respiratory disease may be essential for predicting a beneficial response and minimizing hypoxemia.” The included patients were required to have  $mPAP \geq 35$  mmHg,  $PAWP \leq 15$  mmHg, and  $PVR > 240$  dyn s/cm<sup>5</sup>. The report confirmed that study participants had right ventricle dysfunction “comparable to severe WHO Group 1 PAH” and noted that the included patients had a “moderate degree of restrictive lung disease” with “severe ... superimposed PH.” PH-ILD patients with out-of-proportion PH—such as the “advanced PH” patients in Saggar 2014—might be regarded as having Group 1 PAH.

978. Dr. Rajeev Saggar consistently testified that he was treating the PH component of these patients with out-of-proportion PH.

(5) Dr. Rajan Saggar Did Not Publicly Use Tyvaso Off-Label to Improve Exercise Capacity in PH-ILD Patients

979. Dr. Rajan Saggar did not publicly use Tyvaso off-label with the intended purpose or expectation of improving exercise capacity in PH-ILD patients prior to April 17, 2019.

980. Dr. Rajan Saggar likely only treated patients with PH out of proportion with their underlying lung disease using subcutaneous or intravenous—not inhaled—treprostinil. These patients would likely have been Group 1 PAH patients and not PH-ILD patients with PH “due to” their lung disease as understood by a POSA and according to the 2019 World Symposium guidelines, in which “moderate-to-severe PH” is one criterion favoring Group 1 PAH.

981. The only PH-ILD study published by Dr. Rajan Saggar between 2010 and April 2019, concerning ILD and treprostinil was the Saggar 2014 report. Saggar 2014 involved the administration of intravenous or subcutaneous treprostinil to pulmonary fibrosis patients with advanced PH. Indeed, the report specifically targeted pulmonary fibrosis patients with “advanced

PH,” characterized by “significant altered right heart hemodynamics and right ventricular (RV) dysfunction.” The report acknowledged that “an advanced PH phenotype in the context of chronic respiratory disease may be essential for predicting a beneficial response and minimizing hypoxaemia.” The included patients were required to have  $mPAP \geq 35$  mmHg,  $PAWP \leq 15$  mmHg, and  $PVR > 240$  dyn s/cm<sup>5</sup>. The report confirmed that study participants had right ventricle dysfunction “comparable to severe WHO Group 1 PAH” and noted that the included patients had a “moderate degree of restrictive lung disease” with “severe ... superimposed PH.” PH-ILD patients with out-of-proportion PH—such as the “advanced PH” patients in Saggar 2014—might be regarded as having Group 1 PAH.

982. Dr. Rajan Saggar testified that he appeared on the “I’m aware that I’m rare” podcast on April 8, 2024. During the podcast, Dr. Rajan Saggar stated, “[w]e used a pulmonary hypertension medication to try to work on the pulmonary hypertension complicating the lung problem. And now that’s FDA approved. So it’s the first medication that’s now approved in this particular type of pulmonary hypertension, which is kind of cool.” He testified that he was referring to the approval of Tyvaso for PH-ILD and that the FDA approved medication he was referring to is Tyvaso for PH-ILD. On the podcast, Dr. Rajan Saggar also said:

And it just so turns out that for years we've tried to use different medications to try to treat that type of pulmonary hypertension, specifically complicating the lung tissue diseases. And our attempts have failed several times over; however, there is a recent arrival of a medication that we also use in regular pulmonary hypertension, you know, where you don't have a lung tissue problem, where we were able to use the same medicine, and luckily it actually did work in patients who specifically have this lung tissue problem, this interstitial lung disease or fibrosis or scarring of the lung complicated by pulmonary hypertension.

983. Dr. Rajan Saggar also testified concerning Shino 2013. Shino 2013 was published after Tyvaso was approved for PAH but before it was approved for PH-ILD. Shino 2013 states

that PH-specific therapies in the context of parenchymal lung disease including interstitial lung disease and PH “have been poorly studied, with concern for increased shunting and/or ventilation/perfusion (V/Q) mismatch and resultant hypoxemia.” Dr. Rajan Saggar testified that this is what the authors thought when the publication was written. Shino 2013 further states that “[t]herapies for PH include nitric oxide, prostacyclin analogs, phosphodiesterase inhibitors, ET-1 receptor antagonists, and calcium channel blockers (CCBs).” Dr. Rajan Saggar confirmed that prostacyclin analogs include treprostinil. Shino 2013 recognizes that “[t]hese therapies have been well studied in Group I PAH, but data regarding their use in Group III (IPF-associated PH) . . . are limited to small nonrandomized studies.” Dr. Rajan Saggar testified that IPF-associated PH is PH-ILD. Dr. Rajan Saggar admitted that “therapies including treprostinil had been well studied in Group I PAH” but “the data was limited for Group III including PH-ILD to small studies that were not controlled or randomized.”

984. Shino 2013 then states that “[g]uidelines discouraged the use of these agents due to the lack of data demonstrating efficacy and safety concerns.” Dr. Rajan Saggar testified that the referred to “guidelines” included “guidelines that are put out by various agencies” including, “the European Respiratory Society and European Society of Cardiology guidelines or the World Symposium For Hypertension guidelines.” Dr. Rajan Saggar admitted that “pulmonary hypertension therapies approved for Group I PAH generally are discouraged to the use of Group III PAH at that time.”

985. Shino 2013 states, “[i]n summary, the role of medical pharmacotherapy for IPF-PH has not been well studied and remains controversial. Additional studies are required to determine if some subsets of IPF patients with PH may benefit from PH-specific therapy.” Dr. Rajan Saggar admitted that IPF-PH is the most common type of PH-ILD.

986. Shino 2013 also states:

PH-specific therapies have minimal proven benefit and should be used with caution. Significant PH complicating parenchymal lung disease should trigger a referral for LT. Future studies are necessary to better understand the factors that promote significant PH in the setting of ILD and/or COPD.

987. Dr. Rajan Saggar was a named author on Lynch 2016. The first author of this publication was Joseph P. Lynch III. Lynch 2016 was published after Tyvaso was approved for PAH but before it was approved for PH-ILD. Lynch 2016 states,

The impact of treating PAH in patients with IPF has not been elucidated. The role of PAH-specific agents such as prostacyclin analogs, phosphodiesterase inhibitors, and/or ET-1 receptor antagonists is controversial. Guidelines discouraged the use of these agents due to lack of data demonstrating efficacy, safety concerns, and expense.

988. Lynch 2016 also states that, “[i]n summary, the role of medical pharmacotherapy for IPF-PAH has not been well studied and remains controversial.”

989. Dr. Rajan Saggar testified that PAH-specific agents such as prostacyclin analogues include treprostinil and that IPF-PAH falls within PH-ILD.

990. Lynch 2016 further states that, “[i]n a recent prospective study, 15 patients with pulmonary fibrosis and PAH were treated with parenteral treprostinil, with modest improvement in RV function without worsening hypoxemia.” Dr. Rajan Saggar admitted that this statement was referring to Saggar 2014. Lynch 2016 then recognizes that, “[a]dditional studies are required to assess which patient subsets may benefit from PAH-specific therapies.”

991. Dr. Rajan Saggar was the senior author on Tseng 2018. The first author of this publication was Steve Tseng. Tseng 2018 was published four years after Saggar 2014. Tseng 2018 states, “[t]here is limited evidence supporting the use of PH-specific therapy in COPD and DPLD.” Dr. Rajan Saggar admitted that DPLD includes interstitial lung disease. Rajan Saggar also admitted

that Saggar 2014 does not have any conclusions regarding FVC.

992. Dr. Rajan Saggar co-authored a short letter, *Il Buono* 2014, in response to Dr. Paul Corris' criticism of Saggar 2014. The letter was entitled "*Il Buono, Il Brutto, Il Cattivo*," which means "the good, the bad, and the ugly." *Il Buono* 2014 states, "However, and most critically, the central premise of this manuscript remains simply that the advanced PF-PH phenotype may be particularly receptive to PH-targeted therapy, and this PF-PH subset ought to be considered in future clinical studies." *Il Buono* 2014 states, "[h]owever, and most critically, the central premise of this manuscript remains simply that the advanced PF-PH phenotype may be particularly receptive to PH-targeted therapy, and this PF-PH subset ought to be considered in future clinical studies." The final paragraph then states, "we hope the results (good, bad and ugly) of this small, but important study in 2014, will set the stage for the design of a future clinical trial that hopefully revolutionises the management of patients with PF-PH."

(6) Dr. Channick Did Not Publicly Use Tyvaso Off-Label to Improve Exercise Capacity in PH-ILD Patients

993. Dr. Richard Channick did not publicly use Tyvaso off-label with the intended purpose or expectation of improving exercise capacity in PH-ILD patients prior to April 17, 2019.

994. Dr. Channick testified that until "recently published data"—i.e., INCREASE—"show[ed] efficacy of inhaled treprostinil in patients with ILD with a wider range of PVR impairment," treatment had historically been limited to "patients with severe PH that appeared to be 'out of proportion' to the underlying lung disease." He also testified that only with "recently published data" has it become clear that inhaled treprostinil can be effective for PH-ILD patients without "out of proportion" PH.

995. Dr. Channick likely only administered inhaled treprostinil to ILD patients with severe PH out of proportion with their underlying lung disease, which would likely have been

Group 1 PAH patients and not PH-ILD patients with PH “due to” their lung disease as understood by a POSA and according to the 2019 World Symposium guidelines, in which “moderate-to-severe PH” is one criterion favoring Group 1 PAH.

996. Dr. Channick’s purported off-label use of inhaled treprostinil in PH-ILD patients is not corroborated by or disclosed in any publications.

(7) Dr. Parikh Did Not Publicly Use Tyvaso Off-Label to Improve Exercise Capacity in PH-ILD Patients

997. Dr. Kishan Parikh did not publicly use Tyvaso off-label with the intended purpose or expectation of improving exercise capacity in PH-ILD patients prior to April 17, 2019.

998. Dr. Parikh likely only administered inhaled treprostinil to ILD patients with severe PH out of proportion with their underlying lung disease, which would likely have been Group 1 PAH patients and not PH-ILD patients with PH “due to” their lung disease as understood by a POSA and according to the 2019 World Symposium guidelines, in which “moderate-to-severe PH” is one criterion favoring Group 1 PAH.

999. Dr. Parikh was the first author of Parikh 2016. Parikh 2016 was a retrospective report and “only included patients thought to be good candidates for higher dose [inhaled treprostinil].” Of the 80 patients included in the Parikh 2016 report, only 6 had ILD. A 2021 abstract authored by Dr. Parikh also describes a retrospective study on “patients with PH who were treated with iTre at Duke University between 2009 and 2017” and explains that “all patients had PH (mean pulmonary artery pressure (mPAP)  $\geq$  25mmHg) due to groups 1, 4, or 5, and a subset had mixed disease with group 1 PH and components of groups 2 or 3.” Parikh 2021 implies that these “mixed disease” patients have “PH disproportionate to concomitant . . . lung disease.” Any purported PH-ILD patients treated by Dr. Parikh before April 2019 likely had disproportionate PH and should be classified as PAH patients with, at most, components of Group 3 PH.

1000. Dr. Parikh also testified that he and others at Duke focused on treating ILD patients with out-of-proportion PH.

(8) The State of the Art as of April 2019 Discouraged Use of Tyvaso in PH-ILD Patients

1001. There was no support for the use of inhaled treprostinil to improve exercise capacity in PH-ILD patients before the INCREASE study results were publicly known. Prior to INCREASE, any use of inhaled treprostinil in PH-ILD patients could have only been done with, at most, a hope that the drug would help the patients and not with the intended purpose or expectation of improving these patients' exercise capacity. Belief, personal experience, and biological plausibility are unreliable guides as to whether, keeping all other aspects of treatment the same, using a drug produces better outcomes than not using it.

1002. Prior to INCREASE, physicians, including Drs. Nathan, Hill, Waxman, Tapson, Rajeev Saggarr, Rajan Saggarr, Channick, and Parikh could not have administered Tyvaso to a PH-ILD patient with the intended purpose or expectation of improving exercise capacity in the patient. Before the INCREASE results were publicly known, no one knew or expected that use of inhaled treprostinil would improve exercise capacity in PH-ILD patients. Indeed, skepticism was abundant in the field due to prior unsuccessful clinical trials studying the use of other PAH-approved drugs including, iloprost, sildenafil, bosentan, nintedanib, and riociguat for Group 3 PH patients. In view of the many negative trials and widespread skepticism, healthcare practitioners would have been unlikely to use Tyvaso off-label in PH-ILD patients and would not have done so with the purpose or expectation of improving exercise capacity.

1003. Further, prior to INCREASE, it was unexpected that the administration of inhaled treprostinil would result in increased 6MWD, reduced plasma concentrations of NT-proBNP, reduced exacerbations, reduced clinical worsening events, and improvements in FVC. The

INCREASE results were widely considered to be revolutionary.

1004. Further, any use of inhaled treprostinil in PH-ILD patients before April 2019 would not have necessarily and inevitably resulted in an improvement in exercise capacity because improved exercise capacity and the various other measures required by the Asserted Claims (including increases in 6MWD, reductions in plasma concentration of NT-proBNP, reductions in at least one exacerbations of the interstitial lung disease, reduction of clinical worsening events due to the interstitial lung disease, and improvements in forced vital capacity) would not necessarily and inevitably occur as a result of administering inhaled treprostinil to a PH-ILD patient. For example, the INCREASE results show that not every patient who was administered inhaled treprostinil achieved improved exercise capacity. The INCREASE results also showed that not every patient experiences increases in 6MWD, reductions in NT-proBNP, or improvements in FVC. Indeed, the Tyvaso Label (which discloses and incorporates by reference the INCREASE study results) shows that 13 patients in the INCREASE study experienced a greater than 15% decrease in 6MWD after taking inhaled treprostinil as their first clinical worsening event.

1005. The claimed invention and INCREASE study met a long felt and unmet need for improving exercise capacity in PH-ILD patients through the administration of inhaled treprostinil. Before the INCREASE study, the standard course of treatment for PH-ILD included the provision of supplemental oxygen or, for very severe cases, lung transplant. The INCREASE results significantly changed the way physicians treat and manage PH-ILD. The claimed invention was a significant advancement in this field that addressed a critical gap in care. The clinical success of inhaled treprostinil is evident from the welcoming embrace of this treatment option by healthcare providers, its widespread use, and patient uptake and appreciation of Tyvaso to improve exercise capacity in PH-ILD patients, since its FDA approval for this indication.



(9) Any Alleged Off-Label Use that Was Not Subject to Publication Was Not Sufficiently Public

1006. Any off-label use of inhaled treprostinil in PH-ILD patients by Drs. Channick and Tapson (or any other healthcare providers) were not accessible to the public due to the confidential nature of the doctor-patient relationship and the limited skill and knowledge of the patients who received the treatment. For example, patients would not have been aware of or understood the limitations of the Asserted Claims.

1007. U.S. law does not prohibit physicians from prescribing drugs off-label. However, misrepresenting an off-label prescription as being for an FDA-approved indication to obtain insurance coverage is highly discouraged, and ethically and morally irresponsible.

1008. Healthcare providers strive to ensure they do not take actions that could potentially harm their patients; physicians also seek to not prescribe medications unnecessarily.

1009. The patients purportedly given inhaled treprostinil “off-label” were reported to insurance companies as having PAH (as PH out of proportion with their lung disease). As such, medical insurance companies would not have been in possession of the claimed invention. Insurance companies would not have understood that the inhaled treprostinil was being prescribed to PH-ILD patients, let alone to these patients for the purpose or with the expectation of improving their exercise capacity. Insurance companies would not have permitted such use in PH-ILD patients. Neither would they permit such use in PH-ILD patients for the purpose or with the expectation of improving the patients’ exercise capacity.

1010. Dr. Rajeev Saggar testified that “using an agent in advance of the indication”—i.e., for PH-ILD and not out of proportion PH—“creates challenges in insurance coverage . . . because the drug is not approved for an indication.” Patients with PH out of proportion to their ILD would have likely been regarded as PAH patients by insurance companies, not PH-ILD patients.

1011. Any alleged off-label use was a risk-reward decision made between the patient and physician with an expectation of privacy, because clinicians and staff are ethically and legally obligated to keep their patients' names and treatment confidential.

(10) The Alleged Prior Use of Inhaled Treprostinil to Improve Exercise Capacity in PH-ILD Patients According to the Tyvaso Label Does Not Render the Asserted Claims Invalid

1012. The alleged prior use of inhaled treprostinil to improve exercise capacity in PH-ILD patients according to the Tyvaso Label does not render the claims of the '327 patent invalid.

1013. The alleged prior use of Tyvaso would not disclose to the POSA the administration of inhaled treprostinil with the purpose or expectation of improving exercise capacity in PH-ILD patients.

1014. The purported prior use of Tyvaso does not disclose all the limitations of any of the Asserted Claims.

1015. As discussed above (*supra* at §§ V.D.3–V.D.4), administration of Tyvaso according to the 2009 Tyvaso Label and/or the 2017 INCREASE Study Description do not inherently anticipate claim 1 of the '327 patent. The alleged pre-April 2019 public use and/or sale of Tyvaso to improve exercise capacity in PH-ILD patients did not practice and/or disclose all of the limitations of claim 1 for the same reasons as the 2009 Tyvaso Label and/or the 2017 INCREASE Study Description. Likewise, the alleged public use and/or sale of Tyvaso prior to April 2019 did not practice and/or disclose all of the limitations of the remaining Asserted Claims because each of these claims depend from claim 1.

1016. The alleged prior use and sale cannot and do not disclose and/or necessarily and inevitably practice each and every limitation of the Asserted Claims.

1017. The 2009 Tyvaso Label and the 2017 INCREASE Study Description, alone or in combination, do not disclose or necessarily and inevitably practice each and every limitation of

claims 2-10 and 17-19 of the '327 patent.

1018. For the same reasons that the 2009 Tyvaso Label and the 2017 INCREASE Study Description do not inherently practice and/or disclose the limitations of claims 2-10 and 17-19, the purported prior use and sale of Tyvaso to improve exercise capacity in PH-ILD patients likewise do not inherently disclose these claim limitations.

1019. For the same reasons that the 2009 Tyvaso label does not inherently disclose all of the limitations of claims 11, 15, and 16, the purported prior use and sale of Tyvaso to improve exercise capacity in PH-ILD patients also does not disclose these limitations.

1020. If Liquidia alleges that the 2009 Tyvaso Label and the 2017 INCREASE Study Description represent an obviousness combination, or that the 2017 INCREASE Study Description necessarily and inevitably results in administration of inhaled treprostinil according to the 2009 Tyvaso Label, this combination also does not disclose each and every limitation of any one of the Asserted Claims because neither of these documents disclose or necessarily and inevitably practice the claim 1 limitation "[a] method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease," nor do they disclose or necessarily and inevitably practice the limitations of Asserted Claims 2-11 and 15-19. Further, Liquidia does not describe why a POSA would be motivated to combine these purported prior art references. For the same reasons, the purported prior use and sale of Tyvaso prior to April 2019 would not disclose each and every limitation of any of the Asserted Claims.

**b) The Claimed Invention of the '327 Patent Was Not Ready for Patenting Before April 2019**

1021. The claimed invention of the '327 patent was not ready for patenting prior to April 17, 2019. As of April 17, 2019 claimed invention was not reduced to practice nor had it been disclosed in documents or drawings such that the POSA would have been enabled to practice it.

1022. As of April 2019, neither the inventors nor anyone else had performed a method that satisfied all the limitations of the Asserted Claims nor had anyone determined that the claimed method would work for its intended purpose.

1023. As of the priority date a physician could not have used inhaled treprostinil with the intent or expectation of improving exercise capacity in a PH-ILD patient. Prior to INCREASE, no one knew or expected that inhaled treprostinil could improve exercise capacity in PH-ILD patients.

1024. The INCREASE study results were the first to show that the claimed method would achieve its intended purpose.

1025. As of April 2019, a POSA would have been skeptical of the safety and efficacy of PAH-approved drugs to improve exercise capacity in PH-ILD patients and would have been concerned that the administration of Tyvaso to such patient could cause harm.

1026. A POSA would not prescribe medications “off-label” when they are aware of a study indicating that the medication may be harmful to a patient.

1027. Before prescribing and administering inhaled treprostinil off-label, physicians would check for both negative studies and studies providing sufficient evidence to support its safety and efficacy. Support for the use of inhaled treprostinil to improve exercise capacity of PH-ILD patients was absent prior to INCREASE, while studies of other PAH drugs raised concerns that treprostinil would not be safe and effective.

1028. As of the priority date, numerous unsuccessful clinical trials studying the use of PAH-approved drugs for Group 3 PH, including the ACTIVE study, the STEP-IPF study, the BPHIT study, the INSTAGE study, the RISE-IIP study, the Sildenafil with Pirfenidone study, and the PERFECT study had caused the industry to be skeptical that any PAH-approved therapy could work for PH-ILD patients. The RISE-IIP and PERFECT studies even indicated that PAH-approved

treatments could be harmful for Group 3 PH patients. For example, the PERFECT study showed an increase in serious adverse events as compared to placebo treatment with no indication of improvement in 6MWD.

1029. Liquidia's September 2024 presentation titled, "PH-ILD Screening, Diagnosis, and Future Research" recognizes that many other manufacturers and researchers had tried and failed to develop a drug that could safely and effectively treat PH-ILD patients or improve exercise capacity in PH-ILD patients before INCREASE. A June 8, 2017 email from Dr. Rajan Saggar to UTC attached a presentation confirming that Drs. Rajan Saggar and Rajeev Saggar were also aware of "extensive 'negative' literature re: trials done in pulmonary fibrosis with PAH medications."

1030. Beyond the many early failed studies where PAH drugs were found unsafe and/or ineffective in PH-ILD patients, medical history is replete with examples of drugs which were widely believed to be effective, with a biologically plausible explanation, and that seemed to be borne out by individual experience that ultimately turned out not to produce better outcomes—or even worse outcomes.

1031. For example, flecainide was used to prevent sudden cardiac death in patients with certain unstable arrhythmias called premature ventricular contractions ("PVCs"). It was well established that recurrent PVCs were a risk factor for sudden cardiac death. Flecainide rapidly suppressed PVCs and restored a normal heart rhythm and became the standard of care for treating patients with these unstable arrhythmias. When randomized clinical trials were planned to study the efficacy of flecainide, many doctors would not allow their patients to participate on the theory that flecainide was highly effective and that it would be unethical to allow the possibility that their patients might be randomized to receive placebo. The Cardiac Arrhythmia Suppression Trial definitively showed not only that flecainide was not effective at preventing sudden cardiac death,

but it also actually increased the chance of cardiac death—by a substantial margin—over placebo.

1032. Due to the many failed studies seeking to use PAH in PH-ILD patients, prior to INCREASE, prescribing inhaled treprostinil to improve exercise capacity in PH-ILD patients would have been unsupported by the clinical evidence.

1033. In view of this skepticism, physicians including, but not limited to, Drs. Nathan, Hill, Waxman, Tapson, Rajeev Saggar, Rajan Saggar, Channick, and Parikh would not have administered inhaled treprostinil to a PH-ILD patient with the intended purpose or expectation of improving exercise capacity prior to the INCREASE study. INCREASE (a randomized controlled trial) was the first study to conclusively demonstrate that inhaled treprostinil can be administered to PH-ILD patients to improve their exercise capacity.

1034. Saggar 2014 acknowledges that the use of PH targeted therapy in the setting of PF was controversial.

1035. As of the priority date, industry skepticism concerning the use of treprostinil in PH-ILD patients was rooted in concerns that treprostinil could cause V/Q mismatch and worsening oxygenation in PH-ILD patients.

1036. The claimed invention of the '327 patent—a method of improving exercise capacity in a PH-ILD patient by administering inhaled treprostinil—was neither conceived, nor reduced to practice before the INCREASE study results were unblinded to the inventors in February 2020.

1037. The inventors did not know that inhaled treprostinil would work to improve exercise capacity in PH-ILD patients until after the unblinding of the INCREASE study results in February 2020. Prior to the unblinding, the inventors did not know that inhaled treprostinil would work for this purpose.

1038. Dr. Smith testified that he first knew that UTC “had a method of improving exercise

capacity in PH-ILD patients using inhaled treprostinil” “[a]t the time of unblinding . . . [i]n February 2020.” He also testified that he and others at UTC had doubts concerning the success of INCREASE prior to patient enrollment and the unblinding of its results.

[REDACTED]

1040. Dr. Deng testified that “[b]efore the study unblinding, in general sense you don’t know. Nobody knows whether or not -- what is the result going to turn out after the study unblinding.”

1041. Prior to April 2019, physicians were not prescribing Tyvaso to PH-ILD patients to improve exercise capacity. At best, physicians were prescribing inhaled treprostinil to patients that would be categorized as PAH patients, with PH out-of-proportion to their ILD. No pre-April 2019 data has been identified that physicians could have relied on to have an expectation that any administration of inhaled treprostinil would improve exercise capacity in a PH-ILD patient.

1042. Even if physicians knew that administration of Tyvaso improved exercise capacity in their out of proportion patients having PAH, this outcome was not expected prior to April 2019 in PH-ILD patients.

1043. The purported prior art including, Saggar 2014, Agarwal 2015, and Faria-Urbina 2018, does not demonstrate that the claimed invention was ready for patenting before April 2019. These publications neither disclose nor perform a method that meets all of the limitations of any

of the Asserted Claims, nor do they establish that the claimed invention would achieve its intended purpose of improving exercise capacity in PH-ILD patients through the administration of inhaled treprostinil because, among other reasons:

- All three reports described administration of treprostinil to only a small number of patients without a placebo arm;
- Agarwal 2015 and Faria-Urbina 2018 were not limited to PH-ILD patients and Saggar 2014 was limited to only a small subset of very sick PH-ILD patients. As such, the observed results could not be attributed to the type of patients addressed in the claims of the '327 patent;
- Some reports did not account for patients who dropped out, didn't tolerate the medication, or died; thereby skewing the results;
- Saggar 2014 administered parenteral, not inhaled treprostinil to PH-PF patients;
- Saggar 2014 does not describe or attempt to measure critical endpoints such as a reduction in exacerbations or clinical worsening events and the endpoints it does measure provided results for PH-PF patients following administration of parenteral, not inhaled, treprostinil;
- Agarwal 2015 makes observations only after 6 months of treprostinil administration;
- Agarwal 2015 does not describe or attempt to measure other supportive endpoints including plasma concentrations of NT-proBNP, or clinical worsening events, and FVC;
- Faria-Urbina 2018 does not describe or attempt to measure other supportive endpoints including plasma concentrations of NT-proBNP or clinical worsening events; and
- There was possible cross-over of the same patients reported in the Agarwal 2015 and Faria-Urbina 2018 reports.

1044. The results of these reports are hypothesis generating only and do not demonstrate conception or reduction to practice of the claimed invention. For example, the Faria-Urbina 2018 Supplementary Materials further demonstrate that these reports are merely hypothesis generating at best and that a POSA would not "expect" the results of these studies to be replicated in a large prospective, controlled, clinical study, like INCREASE. Faria-Urbina 2018 included 6MWD results from only 3 ILD patients. The increase in 6MWD from baseline in these patients was not



statistically significant, with a p-value of 0.631. Although the p-value of 3 CPFE patients was statistically significant, it is unlikely that healthcare providers would expect their CPFE patients to experience similar results based on the results of an uncontrolled report with a sample size of 3.

1045. Prior to INCREASE Dr. Waxman had not performed a method that meets all the limitations of the Asserted Claims or determined that the claimed method would work for its intended purpose.

1046. Prior to April 2019, major organizational guidelines for treating PH-ILD and the recommendations from the Sixth World Symposium on Pulmonary Hypertension maintained a negative stance toward the use of PAH drugs in PH-ILD patient to improve their exercise capacity.

1047. Before INCREASE, physicians held significant concerns regarding the safety of medications that induce vasodilation for use in PH-ILD patients. Prior to INCREASE the general understanding in the field was that “vasodilation may induce a worsening hypoxemia in [PH-ILD] patients.”

## **7. Prior Sale**

1048. The Asserted Claims are not invalid due to prior sale.

1049. Tyvaso was not publicly available, prescribed, or sold to improve exercise capacity in PH-ILD patients prior to April 2019.

1050. The claimed invention of the '327 patent, a method of improving exercise capacity in PH-ILD patients using inhaled treprostinil—was not the subject of a commercial offer for sale before April 17, 2019.

1051. Tyvaso was not used with the intended purpose or expectation of improving exercise capacity in PH-ILD patients before April 2019.

1052. Tyvaso was never publicly sold to improve exercise capacity in PH-ILD patients before April 17, 2019.

1053. Tyvaso was not approved for use in the method of improving exercise capacity in PH-ILD patients until after April 2019.

1054. The Tyvaso drug label did not instruct physicians or patients to use inhaled treprostinil to improve exercise capacity in a PH-ILD patient according to the Asserted Claims before April 2019.

1055. Neither Liquidia nor its experts have identified any pre-April 2019 individual sales of Tyvaso by UTC for the advertised use to improve exercise capacity in a PH-ILD patient according to the Asserted Claims.

1056. Physicians, including Drs. Nathan, Hill, Waxman, Tapson, Rajeev Saggar, Rajan Saggar, Channick, and Parikh prescribed inhaled treprostinil to out of proportion PH-ILD patients, better characterized as having Group 1 PAH, and these prescriptions do not show that the claimed invention of the '327 patent was the subject of a commercial offer for sale before April 2019.

1057. Prior to April 17, 2019, UTC and its executives did not promote and/or offer for commercial sale Tyvaso for use in PH-ILD patients to improve their exercise capacity.

1058. UTC did not affirmatively instruct or encourage off-label use of Tyvaso before April 17, 2019.

1059. No actions have been taken by regulatory authorities against UTC or Dr. Martine Rothblatt accusing them of promoting and/or offering, for commercial sale, Tyvaso for the PH-ILD indication prior to April 17, 2019.

1060. Dr. Rothblatt's statements during a 2018 investor call do not demonstrate that UTC commercially offered Tyvaso for sale to improve exercise capacity in PH-ILD patients before April 2019. Dr. Rothblatt's statements are speculative and lack corroborating evidence.

1061. Dr. Rothblatt is not a physician nor is she a POSA. Her comments, while reflective

of her general leadership perspective and corporate optimism, do not provide technical or factual evidence of a prior commercial sale or offer for sale of Tyvaso. UTC did not affirmatively instruct or encourage off-label use of Tyvaso in PH-ILD patients at any time before or after April 2019.

1062. During the 2018 investor call, Dr. Rothblatt stated that “payers don’t just, like, blindly push the pay button on Tyvaso” and noted that “[e]very patient is carefully assessed by payers in ensuring that it’s an appropriate patient that they’re obligated to pay for and not an experimental patient.”

1063. Physicians did not administer Tyvaso to improve exercise capacity in PH-ILD patients before April 2019. If they did, payers would not have authorized or reimbursed such prescriptions for this unapproved use. Neither Liquidia nor its experts provide any corroborating evidence to that physicians or payers acted otherwise.

1064. Neither Liquidia nor its experts have provided any supporting documentation or corroborating evidence to support their assertions that payers were actively funding the use of Tyvaso to PH-ILD patients with the intended purpose or expectation of improving their exercise capacity before April 17, 2019.

1065. Mr. Dean Bunce testified that Dr. Rothblatt told him that UTC was not “promoting or pushing pre-approval promotion for Tyvaso in Group 3” and recognized that “[a]s a company we can’t promote pre-approval promotion.”

1066. Mr. Bunce testified that he was not aware of any off-label use of Tyvaso in PH-ILD patients at any time, including before April 2019. For example, Mr. Bunce testified that he is “not personally aware” when asked if he is “aware of any instance where Tyvaso was used off-label to treat PH-ILD before Tyvaso was approved to treat PH-ILD.”

1067. FAERS public dashboard data does not demonstrate prior sale of Tyvaso to

improve exercise capacity in PH-ILD patients. This data does not demonstrate any instances of physicians' off-label use of Tyvaso to improve exercise capacity in PH-ILD patients.

1068. Even if a commercial offer to sell Tyvaso for use in PH-ILD patients was made before April 2019, the claimed invention was not ready for patenting at any time before April 17, 2019.

**E. The '327 Patent is Not Obvious**

**1. Deposition and Trial Testimony Not Available to the POSA Is Not Relevant to Obviousness**

1069. Obviousness is an objective inquiry into how the POSA would read the literature. The deposition testimony provided in this action by Dr. Waxman, Dr. Tapson, Dr. Rajeev Saggar, Dr. Rajan Saggar, Dr. Faria-Urbina, Dr. Wade, and Dr. Parikh was all provided in 2024 and thus would not have been available to the POSA, and thus is not relevant to the question of obviousness. Dr. Waxman, Dr. Tapson, Dr. Rajeev Saggar, Dr. Rajan Saggar, Dr. Faria-Urbina, Dr. Wade, and Dr. Parikh all are testifying from their own subjective memory, not from the perspective of the POSA reading and interpreting the literature at the relevant time.

1070. With respect to the '793 patent and the parties' prior litigation regarding that patent, the POSA for the '793 patent would have a different perspective than that of the POSA for the '327 patent, since the patents were filed at different times and the definition of the POSA would vary between the references. Therefore, any testimony from the prior litigation involving the '793 patent is not relevant to the obviousness inquiry in this dispute. Yet taking this testimony at face value does not support that the asserted claims are obvious.

**2. Asserted Claims 9-10 of the '327 Patent Are Not Rendered Obvious by the February 2020 Press Release in Combination with Saggar 2014**

1071. The February 2020 Press Release and the '793 patent are not prior art. A discussion of the full disclosure of the February 2020 Press Release is provided in Section V.C.7. A discussion

of the full disclosure and teachings of the '793 patent is provided in Section V.C.8. A discussion of the full disclosure and teachings of Saggar 2014 is provided in Section V.C.2.

1072. The POSA would not have been motivated to combine the February 2020 Press Release with the '793 patent and Saggar 2014. Saggar 2014 does not disclose improvements in FVC let alone a statistically significant improvement in FVC. Also, the dosage, route of administration, and disease in Saggar 2014 are each different from those described in the February 2020 Press Release. For example, Saggar 2014 concerns a select group of PH-ILD patients, whereas the February 2020 Press Release concerns a broader patient group in terms of disease severity. The POSA would not reasonably expect to observe the same effect as Saggar 2014 after changing so many variables. Changing any one of those variables would have an impact on the observed outcomes. Because the POSA would not expect to have that outcome, there would be no reasonable expectation of success. Saggar 2014 does not disclose a significant change in FVC, reporting only a p-value of 0.687—a value that is not considered statistically significant.

1073. The combination of the February 2020 Press Release and Saggar 2014 fails to teach or disclose the limitations of asserted claims 9-10. Saggar 2014 does not disclose a significant change in FVC, reporting only a p-value of 0.687—a value that is not considered statistically significant. Saggar 2014 also does not report an improvement in FVC of at least 20 mL. The February 2020 Press Release is silent regarding FVC.

1074. An inhaled treprostinil treatment effect is required by asserted claims 9 and 10—the “said administering provides” and “said administering improves” claim language reflect that the FVC outcomes are inhaled treprostinil treatment effects. Saggar 2014 fails to disclose any treprostinil treatment effects, and the February 2020 Press Release discloses no results covering FVC. Saggar 2014 and the '327 patent are not an apples-to-apples comparison with respect to the

reported FVC results—the differences are vast. Saggar 2014 because it is a single-arm study only reports a change score. By contrast, the '327 patent provides data regarding an inhaled treprostinil treatment effect. The inhaled treprostinil treatment effect with respect to FVC is absent from both Saggar 2014 and the February 2020 Press Release. For at least that reason, asserted claims 9 and 10 are nonobvious over Saggar 2014 and the February 2020 Press Release.

1075. The POSA would not have had a reasonable expectation of success in achieving the limitations of asserted claims 9-10. Saggar 2014 studies patients administered parenteral treprostinil, not inhaled treprostinil. Dr. Deng and Dr. Waxman do not state that the POSA would expect the combination of the February 2020 Press Release and Saggar 2014 to succeed. Dr. Deng said “there’s a reasonable assumption that probably you can test,” and Dr. Waxman said “we felt it needed to be investigated.” A reasonable hypothesis to test is akin to a hope, and different from a reasonable expectation of success. The POSA would not have a reasonable expectation that a vasodilator would provide any lung function treatment effect in PH-ILD patients let alone an improved FVC treatment effect. Even the INCREASE study employed FVC only as a safety outcome measure.

1076. Saggar 2014 also expressly informs the POSA not to rely on the reported FVC data. Saggar 2014 states that there were no significant changes in PFT parameters following 12 weeks of treprostinil. Saggar 2014 also states that importantly, pulmonary function (i.e., degree of PF) remained unaltered during the study and did not likely confound the study’s findings. These positions from Saggar 2014 speak for themselves.

1077. In view of the limitations of the Saggar 2014 study, and the fact that the February 2020 Press Release does not and cannot fill in the deficiencies of Saggar 2014, an inhaled treprostinil treatment effect with respect to FVC is not in the art that Liquidia cites. The POSA

would not have been motivated to combine Saggar 2014 with the February 2020 Press Release, and there would not have been a reasonable expectation of success at arriving at the claimed methods. Consequently, the POSA would conclude that asserted claims 9-10 are nonobvious.

**3. Asserted Claim 14 of the '327 Patent is Not Rendered Obvious by the February 2020 Press Release in Combination with the '793 Patent**

1078. The February 2020 Press Release and the '793 patent are not prior art. A discussion of the full disclosure of the February 2020 Press Release is provided in Section V.C.7. A discussion of the full disclosure and teachings of the '793 patent is provided in Section V.C.8. A discussion of the full disclosure and teachings of Saggar 2014 is provided in Section V.C.2.

1079. The POSA would not have been motivated to combine the February 2020 Press Release with the '793 patent and Saggar 2014. The dosage, route of administration, and disease in Saggar 2014 are each different from those described in the February 2020 Press Release. The '793 patent does not disclose a specific formulation of inhaled treprostinil or a model of dry power inhaler. The February 2020 Press Release does not disclose the use of a dry powder inhaler, and the POSA would not reasonably believe that a dry powder is interchangeable with a nebulizer. The POSA would not be motivated to use a dry powder inhaler to practice the methods described in the February 2020 Press Release with a reasonable expectation of success.

1080. The POSA would not have had a reasonable expectation of success in achieving the limitations of asserted claim 14. The POSA would not reasonably expect the dry powder described in the context of acute hemodynamics in the '793 patent to improve exercise capacity in a patient with PH-ILD as discussed in the February 2020 Press Release. For at least those reasons the POSA would not have had a reasonable expectation of success in obtaining the results required in asserted claim 14 in view of the '793 patent and February 2020 Press Release.

**4. Asserted Claims 1–3, 11, and 14–19 of the '327 Patent Are Not Rendered Obvious by the '793 Patent in Combination with Faria-Urbina 2018**

1081. A discussion of the full disclosure of the Faria-Urbina 2018 is provided in Sections V.C.6. A discussion of the deficiencies of Faria-Urbina 2018 is provided in Section V.D.2 .The '793 patent is not prior art. A discussion of the full disclosure and teachings of the '793 patent is provided in Section V.C.8. The '793 patent is not prior art.

1082. The USPTO patent examiner considered both Faria-Urbina 2018 and the '793 patent and still allowed the asserted claims to issue.

1083. The POSA would not be motivated to combine the '793 patent—a patent disclosing hemodynamic changes—with Faria-Urbina 2018—a retrospective analysis with numerous limitations—with a reasonable expectation of success. The combination of the '793 patent and Faria-Urbina 2018 does not teach and disclose each limitation of asserted claims 1-3, 11 and 14-19.

1084. The POSA would have no motivation to combine the '793 patent with Faria-Urbina 2018 at least because the POSA would not know which dosing, patient population, formulation, or device aspects of the respective references to combine. This is at least because an inhaled treprostinil treatment effect is absent from Faria-Urbina 2018, and an inhaled treprostinil treatment effect is absent from the '793 patent.

1085. The '793 patent lacks sufficient data about any patients, except that, on average, their PAP was extremely high and their PVR was very high. With pulmonary artery pressures that high, the POSA would have regarded all of these patients as having PAH, which is not the patient population to which the asserted claims are directed, regardless of whether the patients disclosed in the '793 patent also happened to have an element of fibrosis of the lung. The '793 patent also does not disclose administering at least 6 µg of treprostinil per breath to PH-ILD patients.



1086. Resolving the problems of V/Q mismatch in PH-ILD patients would not have motivated the POSA to combine the '793 patent with Faria-Urbina 2018 with a reasonable expectation of success because it was purely speculative as to whether inhaled treprostinil would have been effective to treat pulmonary hypertension without causing V/Q mismatch. If this was not the case, the INCREASE study would not have included safety endpoints like FVC to monitor V/Q mismatch. The studies described in the '793 patent include a minority of patients with PF, but that subset, especially in view of the types of studies described, would not have established to the POSA that there would be no V/Q mismatch concerns. The POSA at the time of invention would therefore not have a reasonable expectation that inhaled treprostinil would resolve the issues of V/Q mismatch over other treatment options, and the POSA would not be motivated to combine Faria-Urbina 2018 with the '793 patent for that reason.

1087. The POSA would not be motivated to combine Faria-Urbina 2018 with the '793 patent with a reasonable expectation of success in view of Wade 200 (*see* Section V.C.10), Parikh 2016 (*see* Section V.C.9), Seeger 2013, Wang 2015, Bajwa 2016, the INCREASE study (*see* Section IV.B, or certain presentations (*see, e.g.,* Sections V.C.11.c), V.C.11.e)) .

1088. The POSA would not look to the abandoned Wade 200 application for a motivation to combine Faria-Urbina 2018 with the '793 patent due to its focus on intravenous treprostinil administration. Wade 200 does not suggest any inhaled treprostinil dosage that would be successful, and a suggestion that treprostinil could be administered through inhalation would not give the POSA a reasonable expectation that the specific dosages and titrations described in the asserted claims would be successful in achieving the endpoints recited in the asserted claims.

1089. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

1090. Parikh 2016 does not disclose the use of inhaled treprostinil to treat PH-ILD patients. Parikh 2016 studies the use of treprostinil in mixed populations, and Parikh 2016 did not draw conclusions regarding the patient population to which the asserted claims are directed.

1091. The POSA, without a successful RCT, would not intend or reasonably expect with a reasonable degree of medical certainty that combining the prior art would demonstrate that inhaled treprostinil works to improve exercise capacity in a PH-ILD patient population. The POSA would know or be informed that the next step forward does not come with a reasonable expectation of success. Faria-Urbina 2018 appropriately voices the limitations of its chart review, advising that the “[r]esults should be interpreted carefully in view of the small sample size.” The authors of Faria-Urbina 2018 concluded that a “potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in large prospective studies.” The POSA would also pay attention to the authors’ warning: “[u]ntil then, [inhaled treprostinil’s] use in Group 3 PH should be cautiously evaluated in specialized PH Centers, after an individualized assessment and risk-benefit consideration.”

1092. The prior art merely demonstrates further studies might be useful to investigate hypotheses. These deficiencies in the prior art also mean that the POSA could not have a reasonable expectation of success of arriving at the asserted claims. There would not have been a reasonable expectation of success that a treatment effect with respect to improved exercise capacity or any of the other claimed outcomes could be achieved even with further clinical study.

1093. The POSA would not be motivated by the ’793 patent. The ’793 patent does not

disclose treatments specific to PH-ILD or describe doses that are effective at improving exercise capacity in PH-ILD patients or any of the other limitations recited in the dependent asserted claims. The '793 patent is directed at affecting hemodynamics in pulmonary hypertension generally. The studies disclosed in the '793 patent only reflect one dose administered during a right heart catheter, offering no relevant guidance to the POSA in that regard. This is entirely distinct from the multi-center, double-blind, randomized, prospective trial that is the INCREASE study. The POSA would not interpret the INCREASE study to correct the '793 patent's deficiencies because the INCREASE study was conducted with a different patient population than that described and claimed in the '793 patent.

1094. The '793 patent also fails to disclose the characteristics of the INCREASE study cohort. Moreover, the 2017 INCREASE Study Description (*see* Section V.C.11.d)) does not teach or disclose the asserted claims. The INCREASE study results, therefore, do not confirm that the proposed dosing regimen in the 2017 INCREASE Study Description, in combination with the '793 patent, would achieve the limitations required by the asserted claims with a reasonable expectation of success.

1095. The proposed dosing regimen described by the abandoned Wade 200 application is different than the regimen in the asserted claims and cannot cure the '793 patent's deficiencies. Wade 200 also provides no data on the effects of inhaled treprostinil on exercise capacity in patients with PH-ILD, and Wade '200 therefore does not demonstrate the intended or expected improvements of the asserted claims.

1096. That UTC—the applicant for the '327 patent—along with other persons affiliated with the INCREASE study began an investigation into the use of treprostinil in connection with PH-ILD would not motivate the POSA to combine Faria-Urbina 2018 with the '793 patent with a

reasonable expectation of success. The mere disclosure of a study (or documents associated with such a study) is not sufficient to provide the POSA with a motivation to combine or a reasonable expectation of success; the fact that a study needs to be performed would itself inform the POSA that the results of the method to be studied are unclear and that the result has yet to be determined. Statements by Drs. Waxman, Tapson, Rothblatt, and others regarding the INCREASE study would not provide the POSA a motivation to combine Faria-Urbina 2018 with the '793 patent with a reasonable expectation of success for the same reasons. The statements of these investigators also must be taken in the broader context of PH-ILD research—the POSA at the time would have a much less optimistic perspective than persons directly involved with the investigation.

1097. Dr. Waxman's statements at the 12<sup>th</sup> John Vane Memorial Symposium would not provide a motivation to combine Faria-Urbina 2018 with the '793 patent with a reasonable expectation of success. Dr. Waxman stated that his studies "provide some support ... that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered." Dr. Waxman's heavily-conditioned statements would at most suggest to the POSA a hypothesis to be tested, which is not the equivalent of a reasonable expectation of success. Other similar statements from Dr. Waxman do not support that the POSA would have been motivated to combine Faria-Urbina 2018 with the '793 patent with a reasonable expectation of success for the same reasons.

1098. Dr. Waxman's letter to FDA, which was not available to the POSA, was an explanation as to why a study to investigate the use of treprostinil in connection with PH-ILD would be appropriate. This type of letter is a necessary part of the drug approval and research process. The POSA would not look to one of these letters and believe that there was a reasonable expectation of success based on their contents. That is at least because they present the

investigator's hypothesis for a proposed treatment and a rational behind the hypothesis, but they do not do more. Dr. Waxman's letter also fails to describe the particular results claimed in the asserted claims, and thus the POSA reading the letter would not have been motivated to combine Faria-Urbina 2018 with the '793 patent to achieve any of the claimed results.

1099. Other doctors' administration of treprostinil to PH-ILD patients would not have motivated the POSA to combine Faria-Urbina 2018 with the '793 patent with a reasonable expectation of success of developing a PH-ILD administration method to improve exercise capacity or achieve any of the other outcomes of the asserted claims.

1100. Faria-Urbina 2018 does not cure the '793 patent's deficiencies. Faria-Urbina 2018 at least fails to disclose results for PH-ILD patients, and therefore the POSA would not have been motivated to combine Faria-Urbina 2018 with the '793 patent with a reasonable expectation of success of developing a PH-ILD administration method to improve exercise capacity or achieve any of the other outcomes of the asserted claims.

**a) Asserted Claim 1 Is Not Obvious Over the '793 Patent in Combination with Faria-Urbina 2018**

1101. The '793 patent does not disclose a method of improving exercise capacity in a patient having PH-ILD. The '793 patent is silent with respect to exercise capacity let alone improvements in exercise capacity. The '793 patent instead is focused on hemodynamic improvement. The '793 patent's examples do not disclose an improvement in exercise capacity, and it is not clear whether these examples describe treating PH-ILD patients. Also, hemodynamic improvement and exercise capacity are not necessarily and inevitably correlated, so the fact that the '793 patent's examples describe hemodynamic improvements is insufficient to determine that the patients also experienced an increase in exercise capacity. The POSA would have known, both on the filing date of the '793 patent and on the filing date of the '327 patent, that hemodynamic

effects do not necessarily and inevitably indicate benefit to a patient, much less benefits in exercise capacity.

1102. None of the data in the '793 patent separate out patients suffering from PH-ILD—instead the disclosed data aggregated patients suffering from multiple other conditions—and thus the POSA would not be able to draw any conclusion regarding the effect of treprostinil specifically on any patients that potentially had PH-ILD. All the measurements on study subjects disclosed in the '793 patent are taken within 3 hours of a single administration of inhaled treprostinil. By contrast all clinical improvements related to exercise capacity cited in the specification of the '327 patent concern improvements over a period of weeks.

1103. The POSA would not reasonably expect PH-ILD to behave similarly to Group 1 PAH because the POSA would know that the differences between Group 1 PAH and Group 3 diseases are substantial enough to cause highly disparate outcomes. The POSA would know that a number of trials had investigated the use of drugs indicated for PAH with other conditions—including Group 3 diseases—and those trials had been largely unsuccessful, and the POSA would therefore not reasonably expect to improve exercise capacity in a patient with PH-ILD using treprostinil.

1104. The '793 patent also does not disclose any dose of inhaled treprostinil as effective for improving exercise capacity in PH-ILD patients. The '793 patent's examples only provide population data that aggregates patients with multiple diseases. None of these examples describe a particular method, including dosage, that would be effective to improve exercise capacity in PH-ILD patients.

1105. Because there is nothing in the '793 patent showing that any PH-ILD patients experienced improved exercise capacity, the '793 patent does not disclose the following limitation

of asserted claim 1: “a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease.”

1106. Claim 1 of the '793 patent does not disclose improvements in exercise capacity or the use of treprostinil on PH-ILD patients. The “therapeutically effective single event dose” of claim 1 of the '793 patent was construed to refer only to the dose required to cause a hemodynamic impact. This is not the same as the “effective amount” of treprostinil in asserted claim 1. Therefore, claim 1 of the '793 patent does not teach every limitation of asserted claim 1.

1107. The POSA practicing the methods described in the '793 patent would therefore not have any expectation of increasing the exercise capacity of a patient with PH-ILD. The amount of treprostinil that would be effective to improve exercise capacity in a PH-ILD patient varies with the patient and the severity of their disease. The POSA would also not have known, based on the '793 patent, what dose (if any) of inhaled treprostinil to administer to a patient with PH-ILD to improve the patient's exercise capacity.

1108. Faria-Urbina 2018 does not cure the '793 patent's deficiencies. The POSA reading Faria-Urbina 2018 would not understand Faria-Urbina 2018 to teach the methods of asserted claim 1 at least because Faria-Urbina 2018 does not disclose any statistically significant results for the PH-ILD patient population.

1109. Faria-Urbina 2018 has a number of limitations that render conclusions concerning the results of administering inhaled treprostinil in patients with PH-ILD misleading and speculative. Among these limitations are: no comparison to comparable patients who could have been but were not prescribed inhaled treprostinil; conclusions based on an extremely small sample size of only 3 ILD patients and 3 CPFE patients; conclusions concerning exercise capacity (6MWD) are based on only half of the patients considered for data analysis; the authors draw no

conclusion concerning any outcomes in PH-ILD patients; and patients that were considered for data analysis had been highly selected from a broader group of PH patients treated with inhaled treprostinil in a manner that would predispose the reported chart review to favorable outcomes. No results are reported on the combined results from the ILD and CPFE patients. Faria-Urbina 2018 does not disclose a method that, when practiced, improves exercise capacity as compared to not practicing the method. Nor does it do so specifically in patients “having pulmonary hypertension associated with interstitial lung disease” as opposed to pulmonary hypertension of other etiologies such as COPD.

1110. Because Faria-Urbina 2018 and the '793 patent do not describe the effect of administering treprostinil to patients with PH-ILD specifically, it is not possible for the combination of Faria-Urbina 2018 and the '793 patent to disclose a method of improving the exercise capacity of a patient having PH-ILD.

**b) Asserted Claims 2-3, 11, and 14-19 Are Not Obvious Over the '793 Patent in Combination with Faria-Urbina 2018**

1111. The combination of Faria-Urbina 2018 and the '793 patent does not disclose each and every limitation of claim 1, and thus asserted claims 2-3, 11, and 14-19, which depend from claim 1, are not obvious. Also, the additional elements of asserted claims 2-3, 11, and 14-19 cannot be found in the '793 patent or Faria-Urbina 2018, and combining the two does not remedy the respective deficiencies.

**(1) Asserted claims 2-3**

1112. The '793 patent does not disclose the method of asserted claim 1, wherein said administering provides a statistically significant increase of a 6MWD in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering or the method of asserted claim 1, wherein said administering increases a 6 minute walk distance of the patient by at least 10 m after 8 weeks, 12



weeks, or 16 weeks of the administering.

1113. The '793 patent does not describe changes in exercise capacity, and thus it cannot disclose either a statistically significant or a 10m change in 6MWD, which includes not teaching a change in 6MWD after 8 weeks, after 12 weeks, or after 16 weeks of administering inhaled treprostinil to PH-ILD patients. The '793 patent does not describe changes in exercise capacity, and thus it cannot disclose either a statistically significant or a 10 m change in 6MWD, which includes not teaching a change in 6MWD after 8 weeks, after 12 weeks, or after 16 weeks of administering inhaled treprostinil to PH-ILD patients.

1114. None of the data in the '793 patent separate out patients suffering from PH-ILD—instead the disclosed data aggregated patients suffering from multiple other conditions—and thus the POSA would not be able to draw any conclusion regarding the effect of treprostinil specifically on any patients that potentially had PH-ILD. The '793 patent discloses no information beyond 180 minutes. The '793 patent also does not describe any effect on exercise capacity, let alone 6MWD. The POSA would understand that there is a difference between hemodynamic effects—the data that the '793 patent exclusively describes—and exercise capacity, and the two are not necessarily and inevitably correlated. The POSA reading the '793 patent would not understand it to teach a method that would result in either a statistically significant improvement or a 10 m improvement in a PH-ILD patient's 6MWD.

1115. Faria-Urbina 2018 does not cure the '793 patent's deficiencies. This is at least because any conclusions in Faria-Urbina 2018 involved a broader and different set of patients—Faria-Urbina 2018 did not assess PH-ILD patients alone. Also, asserted claims 2-3 require that the claimed methods' "administering" step "provide[]" or "increase[]" a parameter. The claims thus do not merely require an increase, they require that the administering cause that increase. Faria-

Urbina 2018 has limitations preventing a conclusion that any methods disclosed therein cause the increases. Faria-Urbina 2018 failed to demonstrate *any* inhaled treprostinil treatment effect, including 6MWD, and the '793 patent fails to cure this deficiency.

1116. Theoretical statistical analyses of Dr. Saggar's or Dr. Tapson's work is irrelevant to this obviousness determination. This is at least because those analyses would be based on treatments not found in the combination of the '793 patent and Faria-Urbina 2018.

**(2) Asserted claims 11 and 14**

1117. The POSA would not believe a dry powder inhaler is interchangeable with a nebulizer. The POSA would also not reasonably expect that the dry powder inhaler described in the context of acute hemodynamics in the '793 patent would be expected to improve exercise capacity in the PH-ILD patient subset of the data presented in Faria-Urbina 2018. The POSA would also not have a reasonable expectation of success in obtaining the results required in asserted claim 14 because the '793 patent does not disclose a specific formulation of inhaled treprostinil or a model of dry powder inhaler. The '793 patent cannot remedy the deficiencies of Faria-Urbina 2018.

1118. Because the combination of Faria-Urbina 2018 and the '793 patent does not render asserted claim 11 obvious that same combination cannot render asserted claim 14, which depends from asserted claim 11, obvious.

**(3) Asserted claims 15-16**

1119. The '793 patent does not disclose the method of asserted claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg and does not disclose the method of asserted claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient. The '793 patent does not describe the method of asserted claim 1 for several reasons

including its lack of disclosure of a dose effective to improve exercise capacity in PH-ILD patients. The '793 patent does not cure the deficiencies of the Faria-Urbina 2018.

1120. Because the combination of Faria-Urbina 2018 and the '793 patent does not render asserted claim 15 obvious that same combination cannot render asserted claim 16, which depends from asserted claim 15, obvious.

**(4) Asserted claims 17-19**

1121. The '793 patent does not disclose the method of asserted claim 1, wherein said administering increases the 6MWD of the patient by at least 10 m after 8 weeks of the administering or by at least 15 after 12 or 16 weeks of the administering.

1122. The '793 patent does not disclose increasing the 6MWD of a patient and discloses no information beyond 180 minutes, and thus the POSA would understand that the '793 patent does not disclose increasing the 6MWD of a patient by at least 10 meters after eight weeks of administration of inhaled treprostinil or increasing the 6MWD of a patient by at least 15 meters after 12 or 16 weeks of administration of inhaled treprostinil.

1123. Asserted claims 17-19 require that the claimed methods' "administering" step to "increase[]" a parameter. The claims thus do not merely require an increase, they require that the administering cause that increase. Faria-Urbina 2018 has limitations preventing a conclusion that any methods disclosed therein cause the increases. Faria-Urbina 2018 failed to demonstrate *any* inhaled treprostinil treatment effect, including 6MWD, and the '793 patent fails to cure this deficiency.

1124. The '793 patent does not cure the deficiencies of Faria-Urbina 2018, and thus the combination of the '793 patent and Faria-Urbina 2018 do not render asserted claims 17-19 obvious.

**5. Asserted Claims 4-10 of the '327 Patent Are Not Rendered Obvious by Faria-Urbina 2018 in combination with the '793 Patent and Saggar 2014**

1125. A discussion of the full disclosure of the Faria-Urbina 2018 is provided in Section V.C.6. A discussion of the deficiencies of Faria-Urbina 2018 is provided in Sections V.D.2, V.E.4. A discussion of the full disclosure and teachings of the '793 patent is provided in Section V.C.8. A discussion of the deficiencies of the '793 Patent is provided in Section V.E.4. The '793 patent is not prior art. The USPTO patent examiner considered both Faria-Urbina 2018 and the '793 patent and still allowed the asserted claims to issue.

1126. A discussion of the full disclosure and teachings of Saggar 2014 is provided in Sections V.C.2. A discussion of the deficiencies of the Saggar 2014 is provided in Sections V.E.2.

1127. The combination of Faria-Urbina 2018 and the '793 patent does not disclose each and every limitation of asserted claim 1, and Saggar 2014 cannot cure these deficiencies. Therefore, asserted claims 4-10, which depend from asserted claim 1, are not obvious.

1128. The limitations of asserted claims 4-10 cannot be found in either the '793 patent, Faria-Urbina 2018, or Saggar 2014. The combination of these cannot cure these deficiencies.

**(1) Asserted claims 4-5**

1129. The '793 patent does not disclose a statistically significant reduction of a plasma concentration of NT-proBNP in the patient for a patient with PH-ILD, after any particular period of time. The '793 patent also does not disclose the method of asserted claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

1130. None of data in the '793 patent exclusively reflect patients suffering from PH-ILD—data from patients with multiple diseases was aggregated—and thus the POSA would not be able to make any conclusions regarding the effect of treprostinil specifically on patients with

PH-ILD using the teachings of the '793 patent. The examples of the '793 patent also do not describe any effect of treprostinil administration on the concentration of NT-proBNP, let alone on patients with PH-ILD.

1131. The POSA would understand that NT-proBNP is associated with certain cardiovascular disorders, but the POSA would also understand that NT-proBNP is not directly correlated with the hemodynamic properties described in the '793 patent. Because the '793 patent does not describe the effects of treprostinil administration on NT-proBNP plasma concentration, the POSA would not understand the '793 patent to teach a method of lowering NT-proBNP concentration.

1132. Saggar 2014 does not describe any effects of inhaled treprostinil. Saggar exclusively concerns parenteral treprostinil. Because Saggar 2014 concerns parenteral treprostinil, the POSA would not have a reasonable expectation that the reduction in NT-proBNP concentration reported in Saggar 2014 would occur if treprostinil was inhaled. The POSA would understand that inhaled administration of treprostinil and parenteral administration of treprostinil have different effects

1133. There were no known correlations between parenteral administration of treprostinil and inhaled administration of treprostinil. There was no known relationship between 6MWD, hemodynamic changes, and NT-proBNP reductions. The lack of a direct relationship between these parameters is the reason why each parameter was measured individually in the prior art analyses and studies. The POSA would not reasonably expect to see the results described in Saggar 2014 after performing the methods of the '793 patent. Saggar 2014 explains that its results require confirmation in a multi-center, randomized study design, and the POSA would understand that to be confirming that Saggar 2014 does not disclose the effects of inhaled treprostinil.

1134. The amounts of treprostinil being administered to the patients in Saggar 2014 (2ng/kg/min and uptitrated by a maximum of 1 ng/kg/min every 12 hours) are different from those described in both the '793 patent and Faria-Urbina 2018. The POSA would not expect to get the results described in Saggar 2014 after using the different dosages and different administration routes described in Faria-Urbina 2018 and the '793 patent.

1135. The authors of Saggar 2014 observed that the Saggar 2014 subjects had an average mPAP>45 mm Hg, a markedly elevated PVR, and degrees of RV dilatation and dysfunction comparable to severe WHO Group I PAH. The Saggar 2014 authors explained that these physiological differences are likely critical when considering the potential response to PH-targeted therapies, given that patients with advanced lung disease in the absence of advanced PH typically do not possess evidence of a circulatory limitation to exercise. In contrast, patients with parenchymal lung disease (COPD or PF) and advanced PH demonstrate (in addition to their inherent ventilatory limitation) a circulatory limitation on exertion and an overall cardiopulmonary exercise stress test profile similar to isolated Group I PAH.

1136. The POSA would understand that the “said administering provides” and “said administering reduces” claim language reflects that the “plasma concentration of NT-proBNP” outcome is an inhaled treprostinil treatment effect. Neither Faria-Urbina 2018 nor the '793 patent teach anything regarding NT-proBNP. Saggar 2014 is also deficient, failing to teach inhaled treprostinil and NT-proBNP. Moreover, Saggar 2014 does not teach a parenteral treprostinil treatment effect.

1137. Because the '793 patent does not describe decreasing a PH-ILD patient's plasma concentration of NT-proBNP, the '793 patent does not remedy the deficiencies of Faria-Urbina 2018. Saggar 2014 also does not remedy the issues of Faria-Urbina 2018, because the POSA would

not be able to reasonably expect how changing both the dosage and administration route for treprostinil would affect the results described in Saggar 2014 and in view of Saggar 2014's other limitations, including its small sample size and lack of control arm. Therefore, the combination of Faria-Urbina 2018, Saggar 2014, and the '793 patent does not render asserted claims 4-5 obvious.

**(2) Asserted claim 6**

1138. The '793 patent does not disclose a statistically significant reduction of at least one exacerbations of the interstitial lung disease for a patient with PH-ILD.

1139. An exacerbation of interstitial lung disease is an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality. The '793 patent does not describe exacerbations of interstitial lung disease; does not describe any measurement of exacerbations of interstitial lung disease; and does not describe how treprostinil could affect such an exacerbation. The '793 patent's examples describe studies performed over short time frames, and thus the POSA would not reasonably expect such studies to be capable of detecting a difference in a patient's risk of exacerbation of interstitial lung disease. The claimed methods of the '793 patent can also be practiced by as little as a single administration of treprostinil, and no clinical impact of a single administration of treprostinil to exacerbations of interstitial lung disease risk had been shown prior to the INCREASE study. The POSA would not reasonably expect that the '793 patent teaches any reduction in exacerbation of interstitial lung disease risk for patients with PH-ILD.

1140. Saggar 2014 does not cure the '793 patent's deficiencies. Saggar 2014 does not describe the effects of inhaled treprostinil—Saggar 2014 instead teaches the use of parenteral treprostinil. Saggar 2014 does not describe a reduction of the risk of exacerbation of interstitial lung disease. Saggar 2014 does not describe a control group against which the POSA could compare a treatment group to detect a treatment effect. The POSA would be unable to determine

if the treatment described in Saggar 2014 resulted in a decrease in the risk of exacerbation of interstitial lung disease, let alone a decrease in exacerbation of interstitial lung disease risk brought about through the administration of inhaled treprostinil.

1141. The amount of treprostinil administered to the patients in Saggar 2014 (2ng/kg/min and uptitrated by a maximum of 1 ng/kg/min every 12 hours) are different from those described in both the '793 patent and Faria-Urbina 2018. The doses recited by the '793 patent include doses of as little as 5 µg per breath of treprostinil. The POSA would not reasonably expect to get the results described in Saggar 2014 after using the different dosage and different administration routes described in Faria-Urbina 2018 and the '793 patent.

1142. An improvement in shortness of breath or an improvement in 6MWD is not sufficient to show a statistically significant reduction in the risk of exacerbation of interstitial lung disease. Different patients can respond differently to a given drug—some might respond well, and some might respond poorly. Showing that on average some patients might have improved 6MWD relative to their previous baseline in a small sample population without a control does not mean that there was a reduction in the risk of exacerbation of interstitial lung disease.

1143. Since the '793 patent does not describe a statistically significant decrease of at least one exacerbations of interstitial lung disease, the '793 patent does not remedy the deficiencies of Faria-Urbina 2018, nor does Saggar 2014 remedy the deficiencies of the '793 patent combined with Faria-Urbina 2018. The combination of Faria-Urbina 2018, the '793 patent, and Saggar 2014 does not render asserted claim 6 obvious.

### **(3) Asserted claims 7-8**

1144. The POSA would understand that clinical worsening is hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death, or a lung transplantation. The '793 patent does not disclose the method of asserted



claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease. The '793 patent does not disclose the method of asserted claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6MWD by more than 15% compared to a baseline 6MWD prior to the administering.

1145. The '793 patent and Saggar 2014 do not describe any measurement of clinical worsening, or how treprostinil could affect such worsening. The '793 patent's examples describe studies performed over short timeframes, and the POSA would not expect such studies to be capable of detecting a reduction in clinical worsening risk. Based on the design of the studies described in the '793 patent, the POSA would not reasonably expect the '793 patent to teach any reduction in clinical worsening risk for patients with PH-ILD. Also, improvements of patient metrics (such as 6MWD) are not synonymous with decreases in clinical worsening risk.

1146. The POSA would understand that the "said administering provides" claim language reflects that the "statistically significant reduction of clinical worsening events due to the interstitial lung disease" outcome is also an inhaled treprostinil treatment effect. Neither Faria-Urbina 2018 nor the '793 patent teach clinical worsening events due to the interstitial lung disease. Also, neither reference teaches an inhaled treprostinil treatment effect with respect to clinical worsening events due to the interstitial lung disease. The POSA would not have a reasonable expectation of success of arriving at the claimed methods. That is at least because a POSA would not reasonably expect treprostinil to have a treatment effect with respect to interstitial lung disease.

1147. Since the '793 patent and Saggar 2014 do not describe a statistically significant reduction in clinical worsening events due to interstitial lung disease, the combination of the '793 patent and Saggar 2014 does not cure the deficiencies of Faria-Urbina 2018. The combination of

Faria-Urbina 2018, Saggar 2014, and the '793 patent do not render asserted claim 7 obvious.

1148. The '793 patent and Saggar 2014 do not describe any measurement of clinical worsening, so the '793 patent and Saggar 2014 do not disclose the particular clinical worsening events described in asserted claim 8—specifically at least one hospitalization for cardiopulmonary indication and a decrease in a 6MWD by more than 15% compared to a baseline 6MWD prior to the administering. The combination of Faria-Urbina 2018, Saggar 2014, and the '793 patent does not render asserted claim 8 obvious.

**(4) Asserted claims 9-10**

1149. The '793 patent does not disclose the method of asserted claim 1, wherein said administering provides a statistically significant improvement of forced vital capacity in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering. The '793 patent also does not disclose the method of asserted claim 9, wherein said administering improves the forced vital capacity in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

1150. The term forced vital capacity refers to the amount of air that can be forcibly exhaled through the lungs after taking the deepest breath possible, as measured by spirometry.

1151. The '793 patent does not discuss forced vital capacity—the '793 patent instead focuses on hemodynamic parameters. The POSA understands that the flow of blood and the flow of air are different properties in different anatomic regions that are not necessarily related. The '793 patent nowhere discusses administering treprostinil over a period of weeks, and the '793 patent fails to disclose long-term dosing of treprostinil to any patient with PH-ILD. The '793 patent instead indicates that the effects of treprostinil are immediate and that the half-life of treprostinil in the body is in the order of hours. Since the '793 patent does not disclose any effect of treprostinil on forced vital capacity, the '793 patent cannot teach a method of using treprostinil to achieve a statistically significant improvement in the forced vital capacity of a patient with PH-ILD after

any particular period of time.

1152. Saggar 2014 does not remedy the deficiencies of the '793 patent. Saggar 2014 does not describe the effects of inhaled treprostinil, and the study reported in Saggar 2014 suffers from additional limitations due to its small sample size and lack of a control group. The POSA would not reasonably expect to get the results purportedly described in Saggar 2014 after using the different dosages and different administration routes described in Faria-Urbina 2018 and the '793 patent. Additionally, the change in FVC described in Saggar 2014 is not statistically significant, and thus it cannot satisfy the requirements of asserted claims 9-10. The POSA would find comparing the FVC change reported in Saggar 2014 and the FVC change reported in the 2021 NEJM Publication facially unreasonable given the difference in p-values.

1153. Saggar 2014 discloses no statistically significant change in FVC nor any specific volume change in FVC. The more recent Faria-Urbina 2018 using inhaled treprostinil reports *reduced* percent predicted FVC. There would be no reasonable expectation of success to achieve an inhaled treprostinil treatment effect with respect to interstitial lung disease.

1154. The '793 patent does not describe a method of providing a statistically significant improvement in forced vital capacity for a patient with PH-ILD; the amount and administration route of treprostinil described in Saggar 2014 is substantially different from that described in Faria-Urbina 2018 and the '793 patent; and the study report in Saggar 2014 suffers from other flaws. The '793 patent and Saggar 2014 do not remedy the deficiencies of Faria-Urbina 2018, and the combination of Faria-Urbina 2018, Saggar 2014, and the '793 patent do not render asserted claims 9-10 obvious.

**6. Asserted Claims 1–3, 7-8, and 14–19 of the '327 Patent Are Not Rendered Obvious by the '793 Patent in Combination with Agarwal 2015**

1155. A discussion of the full disclosure of Agarwal 2015 is provided in Section V.C.4.

UTC's contested facts regarding Faria-Urbina 2018 apply with equal force to Agarwal 2015. A discussion of the full disclosure of the Faria-Urbina 2018 is provided in Section V.C.6. A discussion of the deficiencies of Faria-Urbina 2018 is provided in Sections V.D.2, V.E.4-V.E.5.

1156. A discussion of the full disclosure and teachings of the '793 patent is provided in Section V.C.8. A discussion of the deficiencies of the '793 Patent is provided in Sections V.E.4-V.E.5. The '793 patent is not prior art. The USPTO patent examiner considered Faria-Urbina 2018, Agarwal 2015, and the '793 patent and still allowed the asserted claims to issue. Agarwal 2015 is also explicitly identified in the specification of the '327 patent.

1157. The POSA would not be motivated to combine Agarwal 2015 and the '793 patent. An inhaled treprostinil treatment effect is absent from Agarwal 2015 and absent from the '793 patent. Any disclosure of PH-ILD patients in Agarwal 2015 is only as a subset of a broader patient population, specifically Agarwal 2015 discloses the use of treprostinil in connection with a heterogenous Group 3 PH population of diseases. The patient population described in Agarwal 2015 included both PH-ILD and PH-COPD patients and described increased exercised capacity in both groups. UTC ran Phase III randomized clinical trials with both groups, and only the PH-ILD study (INCREASE) showed a confirmed benefit, while the PH-COPD study (PERFECT) was terminated early for safety concerns with no signal of any benefit.

1158. Agarwal 2015 fails to disclose an inhaled treprostinil treatment effect. Agarwal 2015 cannot disclose an inhaled treprostinil treatment effect because it reports data generated by single-arm, single-center, open-label, retrospective chart review. The POSA would understand or would be informed that this is one of the critical limitations of a single-arm chart review. A single-arm study can only produce change scores—i.e., the differences between patients' respective baselines and follow-up visits. Tests of statistical significance in change scores in patients that

received the same treatment under study (inhaled treprostinil in this chart review) cannot alone be used to draw inferences about the effectiveness of that treatment. The POSA would know or be informed that Agarwal 2015 does not disclose an inhaled treprostinil treatment effect.

1159. The POSA would not expect administration of treprostinil to improve 6MWD in PH-ILD patients based on the teachings of Agarwal 2015 and the '793 patent. Neither Agarwal 2015 nor the '793 patent disclose any results from PH-ILD patients specifically—they each instead disclose broader heterogenous patient populations. The '793 patent's disclosure of patients that fall into the category of PH-ILD, if any, is only as a minor subset of a broader set of PH patients. Therefore, the '793 patent does not provide the POSA any reasonable expectation of success with respect to PH-ILD patients.

1160. The POSA would also not know which aspects of Agarwal 2015 and the '793 patent should be combined. The teachings of the INCREASE study, Faria-Urbina 2018, Wade 200, and Parikh 2016 would not motivate combination of the '793 patent and Agarwal 2015. Statements by UTC, public presentations in the 2017-2018 period, and alleged use by doctors would also not motivate the POSA to combine the '793 patent and Agarwal 2015. Agarwal 2015 and the '793 patent do not disclose treatment of PH-ILD. The POSA would not know what the proposed combination of the '793 patent would look like.

1161. The POSA would not reasonably intend or expect with a reasonable degree of medical certainty that inhaled treprostinil would improve exercise capacity in a PH-ILD patient population without a successful RCT. The POSA would not have had a reasonable expectation of success in arriving at the claimed methods. The POSA would know or be informed that this step does not come with a reasonable expectation of success. Agarwal 2015, which the POSA would recognize as merely an abstract, concludes “[a] prospective trial is indicated.” The POSA would

not be aided by the '793 patent—a patent that does not address exercise capacity (or any other limitations of the dependent asserted claims) at all and for which any PH-ILD data is masked amongst data reported in aggregate. The POSA would also understand that the '793 patent only reflects data from one dose administered during a right heart catheter. Therefore, the POSA would find no guidance relevant or otherwise in the '793 patent. There would not have been a reasonable expectation of success that a treatment effect with respect to improved exercise capacity or any of the other claimed outcomes could be achieved even with further clinical study.

1162. Statements made by UTC's CEO Dr. Rothblatt on a 2018 earnings call would not motivate the POSA to combine the '793 patent with Agarwal 2015 with a reasonable expectation of success. Dr. Rothblatt's statements are referring to the use of inhaled treprostinil to treat Group 3 PH generally, not PH-ILD specifically. Dr. Rothblatt also stated that only "some" Group 3 PH patients saw benefit, but she never explains which—despite explicitly stating that there are at least "2 distinct populations." The POSA would not be motivated to combine references based on such statements, because the POSA would not even know what indication the combination would be successful for. This problem is exacerbated by the series of failed studies that occurred after this call, which would have led the POSA away from any combination to administer treprostinil for PH-ILD. The POSA would also not make a clinical treatment decision based on a company's earnings call to investors or seek to combine any such information with any prior studies without seeing the actual study results that are being alluded to.

1163. The conclusion of Agarwal 2015 is broader than PH-ILD, and therefore without hindsight the POSA would not have had a reasonable expectation of success in any particular subset of the aggregate patient population from Agarwal 2015.

1164. The POSA would have lacked motivation to combine the teaching of a dry powder

inhaler from the '793 patent with Agarwal 2015. Agarwal 2015 reports that inhaled prostanoid therapy is delivered directly to well-ventilated lung units preserving V/Q, and reducing undesirable alterations in perfusion, but the POSA would have been aware that at the time of Agarwal 2015, the only approved inhaled method of administration of treprostinil was with a nebulizer, not with a dry powder inhaler. The POSA would also have been concerned about V/Q mismatch even with an inhaled therapy. Based on Agarwal 2015's teaching that V/Q mismatch can occur if drug is not delivered directly to well-ventilated lung units preserving V/Q, the POSA would have been reluctant to make any change to the delivery mechanism of Agarwal 2015.

1165. The POSA would have been dissuaded from using a dry powder inhaler. The POSA would have been aware that there are drawbacks to the use of a dry powder inhaler in a patient population with damaged lungs, such as patients with PH-ILD. The POSA would not have reasonably expected success of using a dry powder inhaler to administer treprostinil as part of a combination of the '793 patent and Agarwal 2015.

**a) Asserted Claim 1 Is Not Obvious Over the '793 Patent in Combination with Agarwal 2015**

1166. The '793 patent does not disclose a method of improving exercise capacity in a patient having PH-ILD. The '793 patent does not discuss improvements in exercise capacity—the '793 patent focuses on hemodynamic improvement. The '793 patent's examples do not disclose improvements in exercise capacity. It is also not clear that any of the patients treated in either example of the '793 patent suffered from PH-ILD. Hemodynamic improvement and exercise capacity are not necessarily and inevitably correlated, and thus the examples of the '793 patent do not provide sufficient information to determine that the patients also experienced an increase in exercise capacity. None of the data in the '793 patent separate out patients suffering from PH-ILD—instead the disclosed data aggregated patients suffering from multiple other conditions—

and thus it is not possible to make any conclusion regarding the effect of treprostinil specifically on patients with PH-ILD.

1167. There is nothing in the '793 patent disclosing that the treated patients suffered from PH-ILD, and there is nothing in the '793 patent disclosing that the patients in the '793 patent's examples exhibited improved exercise capacity. The '793 patent does not disclose a method of improving exercise capacity in a patient having PH-ILD let alone a particular method that would be effective to improve exercise capacity for patients with PH-ILD. The '793 patent also does not disclose administering an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil to a patient having PH-ILD.

1168. Agarwal 2015 does not remedy any of the deficiencies of the '793 patent. Agarwal 2015 does not distinguish between patients with or without PH-ILD. Agarwal 2015 does not describe titrating the amount of treprostinil provided to the PH-ILD population, let alone that such a population would expect to have an increased exercise capacity as a result. Agarwal 2015 does not disclose administering inhaled treprostinil to a patient having pulmonary hypertension associated with interstitial lung disease intending to improve exercise capacity. The fact that the chart review Agarwal 2015 reports is also a single-center, open label, retrospective chart review introduces further limitations that the POSA would recognize as supporting that Agarwal 2015 does not disclose an inhaled treprostinil treatment effect. The issues arising from these limitations cast doubt on whether, had all the PH-ILD and PH-CPFE patients been evaluated for exercise capacity, there would have been any positive changes at all in exercise capacity.

1169. About 26% (9/35) of the followed patients were not included in the outcome assessments because they discontinued therapy. Those patients that were excluded appear to have been systematically sicker than those ultimately included in the reported results, indicating that the



reported change scores are too optimistic. Only 21 patients had data on change in 6MWD, an unknown number of which had PH-ILD. Sample sizes for other outcome measures such as WHO functional class and BDI were not reported. Such a small sample in and of itself indicates that the data reported by Agarwal 2015 are not representative of PH-ILD patients. There's also concern that the chart review's open label design impacted the reported data, especially since the chart review was carried out at a single site.

1170. The combination of Agarwal 2015 and the '793 patent does not render asserted claim 1 obvious. Because neither Agarwal 2015 nor the '793 patent describe the effect of administering treprostinil to patients with PH-ILD specifically, it is not possible for the combination of those references to disclose a method of improving the exercise capacity of a patient having PH-ILD.

**b) Asserted Claims 2-3, 7-8, 11, and 14-19 Are Not Obvious Over the '793 Patent in Combination with Agarwal 2015**

1171. The combination of Agarwal 2015 and the '793 patent does not disclose each and every limitation of asserted claim 1, and thus asserted claims 2-3, 7-8, 11, and 14-19, which depend from asserted claim 1, are not obvious. Also, the additional elements of asserted claims 2-3, 7-8, 11, and 14-19 cannot be found in the '793 patent or Agarwal 2015, and combining the two does not remedy the respective deficiencies.

**(1) Asserted claims 2-3**

1172. The '793 patent does not disclose the method of asserted claim 1, wherein said administering provides a statistically significant increase of a 6MWD in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering or the method of asserted claim 1, wherein said administering increases a 6MWD of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.

1173. None of the data in the '793 patent separate out patients suffering from PH-ILD—instead the disclosed data aggregates patients with multiple disease—it is not possible to make any conclusion regarding the effect of treprostinil specifically on patients with PH-ILD using the teachings of the '793 patent.

1174. The examples of the '793 patent do not describe any effect on exercise capacity, let alone 6MWD. The metrics used by the '793 patent to determine the effect of treprostinil administration were hemodynamics. The '793 patent discloses no information beyond 180 minutes. The POSA would understand that there is a difference between hemodynamic effects and exercise capacity, and that the two are not necessarily and inevitably correlated. The POSA would not understand the '793 patent to teach a method that would result in a statistically significant improvement in a patient's 6MWD.

1175. The '793 patent does not describe changes in exercise capacity, and the '793 patent does not disclose a statistically significant or a 10 m change in 6MWD or a change in 6MWD after 8 weeks, 12 weeks, or 16 weeks of administering inhaled treprostinil.

1176. Also, asserted claims 2-3 require that the claimed methods' "administering" step "provide[]" or "increase[]" a parameter. The asserted claims thus do not merely require an increase, they require that the administering cause that increase. Agarwal 2015 has limitations preventing a conclusion that any methods disclosed therein cause the increases. Agarwal 2015 failed to demonstrate *any* inhaled treprostinil treatment effect, including 6MWD, and the '793 patent fails to cure this deficiency.

1177. The '793 patent does not describe a statistically significant or 10 m increase in 6MWD, and thus it cannot cure the deficiencies of Agarwal 2015. Therefore, the combination of Agarwal 2015 and the '793 patent does not render asserted claims 2 and 3 obvious.

**(2) Asserted claims 7-8**

1178. The '793 patent does not disclose a statistically significant reduction of clinical worsening events due to the interstitial lung disease for a patient with PH-ILD. The '793 patent also does not disclose the method of asserted claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in 6MWD by more than 15% compared a baseline 6MWD prior to the administering.

1179. The POSA would understand that clinical worsening is hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death or a lung transplantation. The '793 patent does not describe any measurement of clinical worsening, or how treprostinil could affect such worsening. The '793 patent's examples describe studies performed over relatively short timeframes, and the POSA would not expect such studies to be capable of detecting a reduction in clinical worsening risk. Based on the study design of the '793 patent, the POSA would not expect the '793 patent to teach any reduction in clinical worsening risk for patients with PH-ILD. Since the '793 patent does not describe a statistically significant reduction in clinical worsening events due to interstitial lung disease, the '793 patent does not remedy the deficiencies of Agarwal 2015. The combination of Agarwal 2015 and the '793 patent does not render asserted claim 7 obvious.

1180. The POSA would understand that the "said administering provides" claim language reflects that the "statistically significant reduction of clinical worsening events due to the interstitial lung disease" outcome is also an inhaled treprostinil treatment effect. Neither Agarwal 2015 nor the '793 patent teach clinical worsening events due to the interstitial lung disease. Also, neither reference teaches an inhaled treprostinil treatment effect with respect to clinical worsening events due to the interstitial lung disease. The POSA would not have a reasonable expectation of success of arriving at the claimed methods. That is at least because the POSA would not reasonably

expect treprostinil to have a treatment effect with respect to interstitial lung disease.

1181. The '793 patent also does not disclose the particular clinical worsening events described in asserted claim 8—specifically at least one hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared to a baseline 6-minute walk distance prior to the administering. Because the '793 patent does not describe clinical worsening due to interstitial lung disease, the '793 patent does not remedy the deficiencies of Agarwal 2015. The combination of Agarwal 2015 and the '793 patent does not render asserted claim 8 obvious.

**(3) Asserted claims 11 and 14**

1182. The '793 patent does not disclose the method of asserted claim 1, wherein said administering is performed by a pulsed inhalation device. The '793 patent also does not disclose the method of asserted claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.

1183. The '793 patent does not describe the method of asserted claim 1, and thus the '793 patent does not remedy the deficiencies of Agarwal 2015 and the combination of Agarwal 2015 and the '793 patent does not render asserted claim 11 obvious. Because Agarwal 2015 and the '793 patent do not render asserted claim 11 obvious, the combination of Agarwal 2015 and the '793 patent do not render asserted claim 14 obvious.

**(4) Asserted claims 15-16**

1184. The '793 patent does not disclose the method of asserted claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg.

1185. The '793 patent does not describe the method of asserted claim 1 of the '327 patent. The '793 patent does not remedy the deficiencies of Agarwal 2015, and thus the combination of

Agarwal 2015 and the '793 patent does not render asserted claim 15 obvious.

1186. The '793 patent does not disclose the method of asserted claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient.

1187. The '793 patent does not describe the method of asserted claim 15. Therefore the '793 patent does not remedy the deficiencies of Agarwal 2015, and thus the combination of Agarwal 2015 and the '793 patent does not render asserted claim 16 obvious.

**(5) Asserted claims 17-19**

1188. The '793 patent does not disclose the method of asserted claim 1, wherein said administering increases a 6MWD of the patient by at least 10 m after 8 weeks of the administering; the method of asserted claim 1, wherein said administering increases a 6MWD of the patient by at least 15 m after 12 weeks of the administering, or the method of asserted claim 1, wherein said administering increases a 6MWD of the patient by at least 15 m after 16 weeks of the administering.

1189. The '793 patent does not disclose increasing the 6MWD of a patient, and the '793 patent does not disclose increasing the 6MWD of a patient by 10 or 15 meters. The POSA would therefore understand that '793 patent does not disclose increasing the 6MWD of a patient by at least 10 meters after eight weeks from administration, or at least 15 meters after 12 or 16 weeks from administration. The '793 patent discloses no information beyond 180 minutes.

1190. Asserted claims 17-19 require that the claimed methods' "administering" step to "increase[]" a parameter. The asserted claims thus do not merely require an increase, they require that the administering cause that increase. Agarwal 2015 has limitations preventing a conclusion that any methods disclosed therein cause the increases. Agarwal 2015 failed to demonstrate *any* inhaled treprostinil treatment effect, including 6MWD, and the '793 patent fails to cure this deficiency.

1191. Because the '793 patent does not describe improving a PH-ILD patient's 6MWD by 10 m after 8 weeks of administration, or at least 15 meters after 12 or 16 weeks from administration, the '793 patent does not remedy the deficiencies of Agarwal 2015. Therefore, the combination of Agarwal 2015 and the '793 patent do not render asserted claims 17–19 obvious.

**7. Asserted Claims 4-6 and 9-10 of the '327 Patent Are Not Rendered Obvious by Agarwal 2015 in combination with the '793 Patent and Saggar 2014**

1192. A discussion of the full disclosure of Agarwal 2015 is provided in Section V.C.4. A discussion of the deficiencies of Agarwal 2015 is provided in Section V.E.6. UTC's contested facts regarding Faria-Urbina 2018 apply with equal force to Agarwal 2015. A discussion of the full disclosure of the Faria-Urbina 2018 is provided in Section V.C.6. A discussion of the deficiencies of Faria-Urbina 2018 is provided in Sections V.D.2, V.E.4-V.E.5.

1193. The '793 patent is not prior art. A discussion of the full disclosure and teachings of the '793 patent is provided in Section V.C.8. A discussion of the deficiencies of the '793 Patent is provided in Sections V.E.4-V.E.5. The '793 patent is not prior art.

1194. A discussion of the full disclosure and teachings of Saggar 2014 is provided in Section V.C.2. A discussion of the deficiencies of the Saggar 2014 is provided in Sections V.E.2, V.E.5.

1195. The USPTO patent examiner considered Faria-Urbina 2018, Agarwal 2015, and the '793 patent and still allowed the asserted claims to issue. Agarwal 2015 is also explicitly identified in the specification of the '327 patent.

1196. The combination of Agarwal 2015 and the '793 patent does not disclose each and every limitation of asserted claim 1, and Saggar 2014 cannot cure these deficiencies. Therefore, asserted claims 4-6 and 9-10, which depend from asserted claim 1, are not obvious.

1197. The elements of asserted claims 4-6 and 9-10 cannot be found in either the '793

patent, Saggar 2014, or Agarwal 2015. Asserted claims 4-6 and 9-10 are not rendered obvious because (i) there is no motivation to combine the '793 patent with Agarwal 2015 and Saggar 2014 such that the combination would provide the POSA with a reasonable expectation of success, and the combination does not teach and disclose each limitation.

1198. The combination of Agarwal 2015 and the '793 patent does not disclose each and every limitation of asserted claim 1. None of these references provide data that would cause the POSA to reasonably expect the claimed methods to improve exercise capacity in PH-ILD patients. The '793 patent does not mention exercise capacity. Agarwal 2015 and Saggar 2014 describe uncontrolled, no-placebo studies of a small number of patients, and thus the reported data is not reliable and is hypothesis-generating at best, e.g., by 2020 the field was littered with examples of PAH drugs that showed promise in PH-ILD based on small, uncontrolled studies only to fail when subjected to a randomized clinical trial. Agarwal 2015 and Saggar 2014 explicitly acknowledge their limitations, with Agarwal 2015—which might have included patients with a PAH phenotype—recommending a prospective clinical trial to robustly evaluate its findings and Saggar 2014—which also included patients with PH comparable to PAH and used parenteral, not inhaled treprostinil—describing its findings as “only hypothesis generating.” Saggar 2014 and Agarwal 2015 do not make up for their respective deficiencies and fail to remedy the '793 patent's deficiencies. The combination of the '793 patent, Agarwal 2015, and Saggar 2014 cannot render obvious any of the asserted claims that depend from asserted claim 1, and thus the combination of Agarwal 2015, Saggar 2014, and the '793 patent do not render obvious asserted claims 4-6 and 9-10.

1199. Agarwal 2015 does not disclose the elements of the asserted claims 4-6 and 9-10. Because Agarwal 2015 does not disclose these elements, these elements must be found in either

the '793 patent or Sagggar 2014 to render the asserted claims obvious. The '793 patent and Sagggar 2014 do not cure these deficiencies. Neither the '793 patent nor Agarwal 2015 discusses the exacerbations of interstitial lung disease of asserted claim 6. Acute exacerbations are defined by rapid, idiopathic declines in lung function, patients may report subjective improvement one day, and experience an exacerbation the next. The POSA would thus understand Agarwal 2015 to not teach a statistically significant decline in exacerbations of interstitial lung disease. As for asserted claims 9-10, Sagggar 2014 has grave limitations and none of Sagggar 2014's patients received inhaled treprostinil. The POSA would not have reasonably expected an increase in FVC in PH-ILD patients from inhaled treprostinil based on Sagggar 2014, let alone the claimed statistically significant increase.

1200. The conclusions of Agarwal 2015 are broader than PH-ILD, and therefore Agarwal 2015 in the absence of hindsight would not have provided the POSA a reasonable expectation of success in any subset of the aggregated patient population. The POSA would not intend or reasonably expect with a reasonable degree of medical certainty that inhaled treprostinil works to improve exercise capacity in a PH-ILD patient population based upon these heterogenous and broader patient populations without a successful RCT.

1201. The POSA would not have been motivated to combine Sagggar 2014 with Agarwal 2015 and the '793 patent with a reasonable expectation of success, because none of patients in Sagggar 2014 received inhaled treprostinil. The POSA would have been aware that the impact of an inhaled drug versus a systemically administered drug in patients with pre-existing lung disease, such as patients with PH-ILD, would require caution. Neither the '793 patent nor Agarwal 2015 mention FVC, and thus the POSA would not have looked to either of '793 patent or Agarwal 2015. While the patients in Sagggar 2014 may have had lung disease, Sagggar 2014 reports that the patients



had degrees of RV dilatation and dysfunction comparable to severe WHO Group I PAH. As disclosed by Sagggar 2014: *All 15 patients had baseline mPAP  $\geq 35$  mm Hg; 10 (66%) had mPAP  $\geq 40$  mm Hg and 7 (47%) had mPAP  $\geq 50$  mm Hg.* Thus, the POSA might have regarded the effect of treprostinil to be due to patients who had a PAH phenotype.

1202. The POSA would not be motivated to combine the '793 patent, Agarwal 2015, and Sagggar 2014 with a reasonable expectation of success because of the numerous failed studies and skepticism regarding the efficacy of treprostinil for PH-ILD before the '327 patent. Small, uncontrolled, pilot studies like Agarwal 2015 and Sagggar 2014 could provide no more than a hypothesis that inhaled treprostinil could improve exercise capacity for PH-ILD patients, and the POSA would appreciate that in this field a properly controlled study would be needed to demonstrate that a drug was actually effective. Improving exercise capacity of PH-ILD patients is highly unpredictable.

1203. The elements missing from Agarwal 2015 cannot be found in either the '793 patent or Sagggar 2014. Because none of the '793 patent, Sagggar 2014, or Agarwal 2015 disclose those elements, the combination of Agarwal 2015, Sagggar 2014, and the '793 patent cannot render the asserted claims obvious.

**(1) Asserted claims 4-5**

1204. The '793 patent does not disclose a statistically significant reduction of a plasma concentration of NT-proBNP in the patient for a patient with PH-ILD after any particular period of time. The '793 patent also does not disclose the method of asserted claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

1205. None of the data in the '793 patent separate out those patients suffering from PH-ILD—instead the data aggregated patients with multiple disease—it is not possible to make any

conclusion regarding the effect of treprostinil specifically on patients with PH-ILD along any particular axis using the teachings of the '793 patent.

1206. The '793 patent's examples also do not describe any effect of treprostinil administration on the concentration of NT-proBNP, let alone on patients with PH-ILD. NT-proBNP is associated with certain cardiovascular disorders, but the POSA understands that NT-proBNP is not directly correlated with the hemodynamic properties described in the '793 patent. Since the '793 patent does not describe the effects of treprostinil administration on NT-proBNP plasma concentration, the POSA would not understand the '793 patent to teach a method of lowering NT-proBNP concentration.

1207. Saggar 2014 does not describe the effects of inhaled treprostinil—Saggar 2014 instead teaches the use of parenteral treprostinil. While Saggar 2014 describes a reduction in NT-proBNP concentration, Saggar 2014 would not lead the POSA to reasonably expect that such a reduction would also occur based on the administration of inhaled treprostinil. Inhaled administration of treprostinil and parenteral administration of treprostinil would be expected to have different effects.

1208. The amounts of treprostinil being administered to the patients in Saggar 2014 (2ng/kg/min and uptitrated by a maximum of 1 ng/kg/min every 12 hours) are different from those described in both the '793 patent and Agarwal 2015. The POSA would not expect to get the results described in Saggar 2014 after using the different dosages and different administration routes described in Agarwal 2015 and the '793 patent.

1209. Saggar 2014 discloses the use of treprostinil in connection with interstitial lung disease patients that had severe PH which could be regarded as disproportionate to the extent of their lung disease, and were not typical PH-ILD patients who tend to have more mild-to-moderate

PH. The authors of Sagggar 2014 observed that the Sagggar 2014 subjects had an average mPAP>45 mm Hg, a markedly elevated PVR, and degrees of RV dilatation and dysfunction comparable to severe WHO Group I PAH. The Sagggar 2014 authors explained that these physiological differences are likely critical when considering the potential response to PH-targeted therapies, given that patients with advanced lung disease in the absence of advanced PH typically do not possess evidence of a circulatory limitation to exercise. In contrast, patients with parenchymal lung disease (COPD or PF) and advanced PH demonstrate (in addition to their inherent ventilatory limitation) a circulatory limitation on exertion and an overall cardiopulmonary exercise stress test profile similar to isolated Group I PAH.

1210. The POSA would also understand that the “said administering provides” and “said administering reduces” claim language reflects that the “plasma concentration of NT-proBNP” outcome is also an inhaled treprostinil treatment effect. In this regard, neither Agarwal 2015 nor the ’793 patent teach anything regarding NT-proBNP. Sagggar 2014 is also deficient, failing to teach inhaled treprostinil and NT-proBNP. Moreover, Sagggar 2014 as detailed above does not teach a parenteral treprostinil treatment effect.

1211. Because the ’793 patent does not describe decreasing a PH-ILD patient’s plasma concentration of NT-proBNP, the ’793 patent does not remedy the deficiencies of Agarwal 2015. Sagggar 2014 also does not remedy the issues of Agarwal 2015 because the POSA would not be able to reasonably expect how changing both the dosage and administration route for treprostinil would affect the results described in Sagggar 2014. Therefore, the combination of Agarwal 2015, Sagggar 2014, and the ’793 patent does not render asserted claims 4 and 5 obvious.

## **(2) Asserted claims 6**

1212. The ’793 patent does not disclose a statistically significant reduction of at least one exacerbation of the interstitial lung disease for a patient with PH-ILD.

1213. An exacerbation of interstitial lung disease is an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality. The '793 patent does not describe exacerbations of interstitial lung disease, any measurement of the exacerbation of interstitial lung disease, or how treprostinil could affect such an exacerbation. The '793 patent's examples describe studies performed over relatively short time frames, and the POSA would not expect such studies to be capable of detecting a difference in exacerbation reduction. Based on the study design of the '793 patent, the POSA would not expect the '793 patent to teach any reduction in exacerbation of interstitial lung disease for patients with PH-ILD.

1214. Saggar 2014 does not describe the effects of inhaled treprostinil, only that of treprostinil administered as a continuous infusion under the skin or intravenously (collectively referred to as "parenterally"). Saggar 2014 also does not describe a reduction in the exacerbations of interstitial lung disease related. Saggar 2014 does not describe a control group against which the POSA could compare to detect decreases in exacerbation in the interstitial lung disease. Thus, the POSA would be unable to determine if the treatment described in Saggar 2014 resulted in a decrease in exacerbation risk, let alone a decrease in exacerbation of the interstitial lung disease brought about through the administration of inhaled treprostinil.

1215. The amounts of treprostinil being administered to the patients in Saggar 2014 (2ng/kg/min and uptitrated by a maximum of 1 ng/kg/min every 12 hours ) are different from those described in both the '793 patent and Agarwal 2015. The POSA would not have reasonably expected to get the results described in Saggar 2014 after using a different dosage and different administration route as described in Agarwal 2015 and the '793 patent.

1216. Neither Agarwal 2015 nor the '793 patent explicitly mention acute exacerbations of interstitial lung disease. Most of the patients in the '793 patent and in Agarwal 2015 did not

have interstitial lung disease at all. Although Agarwal 2015 reported that 30 patients had subjective improvement, this does not teach a statistically significant reduction of at least one exacerbation of the interstitial lung disease. These are two different endpoints, and the POSA would not have read a subjective improvement by some, but not all, patients, to indicate a reduction in acute exacerbations of interstitial lung disease. Additionally, thirty patients reported subjective improvement, but not all of them even remained in the study for 6 months.

1217. Acute exacerbations are defined by rapid, idiopathic decline in lung function, such that patients who reported subjective improvement one day might begin experiencing an acute exacerbation on the very next day. For this reason, the POSA would not have read the disclosures of Agarwal 2015 to teach a statistically significant decline in acute exacerbations of ILD. Finally, it is not reported whether these patients had ILD or COPD, and thus, the POSA would not have known whether patients who reported subjective improvement even had ILD.

1218. The '793 patent and Saggar 2014 do not describe a statistically significant decrease of at least one exacerbations of interstitial lung disease, and thus the '793 patent and Saggar 2014 do not remedy the deficiencies of Agarwal 2015. Therefore, the combination of Agarwal 2015, Saggar 2014, and the '793 patent do not render dependent claim 6 obvious.

### **(3) Asserted claims 9-10**

1219. The '793 patent does not disclose the method of asserted claim 1, wherein said administering provides a statistically significant improves of forced vital capacity in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering. The '793 patent also does not disclose the method of asserted claim 9, wherein said administering improves the forced vital capacity in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

1220. The term forced vital capacity refers to the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible, as measured by spirometry.

1221. The '793 patent does not discuss forced vital capacity—the '793 patent focuses on hemodynamic parameters, which relate to the flow of blood as opposed to air. The POSA would understand that the flow of blood and the flow of air are different properties that are not necessarily and inevitably related. The '793 patent does not disclose any effect of treprostinil on the forced vital capacity, the '793 patent cannot teach a method of using treprostinil to achieve a statistically significant improvement in the forced vital capacity of a patient with PH-ILD, after any particular period of time.

1222. Saggar 2014 does not remedy these deficiencies. Saggar 2014 does not describe the effects of inhaled treprostinil. Saggar 2014 instead teaches the use of parenteral treprostinil. The amounts of treprostinil being administered to the patients in Saggar 2014 (2ng/kg/min and uptitrated by a maximum of 1 ng/kg/min every 12 hours) are different from those described in both the '793 patent and Agarwal 2015. The POSA would not have reasonable expectation to get the results described in Saggar 2014 after using a different dosage and different administration route as described in Agarwal 2015 and the '793 patent.

1223. Saggar 2014 does not disclose a statistically significant increase in FVC as required by asserted claims 9 and 10. Saggar 2014 reports that an FVC of 62% of predicted at baseline and 63% 12 weeks later. Given the variability in this measure, these numbers are essentially the same. The p-value attesting to the difference is cited as *0.687*, which is not even statistically significant. The POSA would have been aware that FVC is a measure with significant test-test variability, and Saggar 2014 lacked a control group. The Saggar 2014 authors acknowledged that the absence of a placebo arm was a particularly significant limitation to their findings. The POSA would likely have disregarded Saggar 2014's report of an increase in FVC as noise.

1224. Because the '793 patent does not describe a method of providing a statistically

significant improvement in forced vital capacity for a patient with PH-ILD, and because the amount and administration route of treprostinil described in Saggar 2014 is substantially different from that described in Agarwal 2015 and the '793 patent, the '793 patent and Saggar 2014 do not remedy the issues of Agarwal 2015. The combination of Agarwal 2015, Saggar 2014, and the '793 patent do not render asserted claim 9 obvious. Therefore, the combination of the '793 patent, Saggar 2014, and Agarwal 2015 also does not disclose the method of asserted claim 9, wherein said administering improves the forced vital capacity in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering, and therefore cannot render asserted claim 10 obvious.

## **8. Secondary Considerations Support Non-obviousness**

### **a) There Existed Long-felt but Unsolved Needs Solved by the Claims of the '327 patent**

1225. The claims of the '327 Patent satisfied a long-felt and unmet need. PH-ILD has profound implications for morbidity and mortality, leading to worse functional impairment, increased need for supplemental oxygen, greater health care resource utilization, and a lower survival rate, yet no treatment has ever been approved for its treatment.

1226. Numerous other attempts were made to develop a safe and effective FDA approved treatment for PH-ILD, to no avail.

1227. Prior to the approval of Tyvaso, the standard of care to treat a PH-ILD patient involved supplemental oxygen with a select few patients receiving lung transplants.

1228. Physicians in the PH-ILD space, including Dr. Robert Rantz and Dr. Waxman noted that prior to INCREASE, there were no approved treatments for PH-ILD.

1229. The '793 patent fails to disclose many of the claimed elements of the claimed invention of the '327 patent and, therefore, could not have satisfied the long felt and unmet need for a PH-ILD therapeutic that improves exercise capacity PH-ILD patients.

1230. The basis for the FDA’s approval of the PH-ILD indication was INCREASE. The definition of “treating” in the ’793 patent included all hemodynamic improvements, regardless of whether they resulted in an increase in exercise capacity or any other clinically relevant outcome. There can be a need for hemodynamic improvement satisfied by the ’793 patent that nevertheless failed to fulfill the additional, significant long-felt but unmet need to improve exercise capacity in patients with PH-ILD. For example, the improvement in 6MWD in the INCREASE study could be conceptualized as how far a patient has to walk to perform everyday tasks, such as walking to their mailbox or to their parking spot, in which case 20 meters matters. The ’793 patent discloses no comparable improvements. In contrast, the INCREASE results formed the foundation for the claimed invention of the ’327 patent. Only the claimed invention of the ’327 patent discloses the elements necessary to address the long felt and unmet need for a method of administration to improve exercise capacity, increase 6MWD, reduce NT-proBNP levels, reduce exacerbations, reduce clinical worsening events, and increase FVC following administration of inhaled treprostinil in a PH-ILD patient.

1231. The nexus between the long felt need and the claims of the ’327 patent lie in the results of INCREASE—improve exercise capacity in PH-ILD patients increases in 6MWD, reductions in plasma concentrations of NT-proBNP, reductions in exacerbations, reductions in clinical worsening events, and improved FVC—all of which are embedded within the claimed invention of the ’327 Patent. These results satisfy the long-felt and unmet need for a medication for this purpose.

**b) Prior Art Teaches Away from the Invention**

1232. The prior art teaches away from the subject matter claimed in the ’327 Patent. For example, of the Iloprost (ACTIVE) study, the STEP-IPF study, The BPHIT study, the INSTAGE study, and the RISE-IIP study all failed, which demonstrate the significant failures and limitations



associated with developing a safe and effective treatment for PH-ILD patients.

1233. Previous clinical studies in Group 3 patients following the administration of other PAH drugs had to be terminated early due to safety concerns, for example, the RISE-IIP study, which was terminated early due to increased serious adverse events.

1234. Numerous prior studies tried and failed to safely and effectively treat PH-ILD, let alone develop a method for improving exercise capacity in PH-ILD patients yet the claimed invention achieved what the prior studies could not—demonstrating that the teaching away of the prior art is tied to the claims of the '327 Patent.

**c) Skepticism**

1235. A POSA would be skeptical that Tyvaso would improve exercise capacity in PH-ILD patients. This is largely driven by the prior studies that did not yield successful results.

1236. The outlook on PH-ILD outcomes was negative and a POSA would demand a successful clinical trial due to the prior failed studies.

1237. A POSA would have been skeptical that Tyvaso would improve FVC in PH-ILD patients. This is evidenced by the statements of Drs. Waxman and Smith.

1238. Previous clinical studies assessing FVC in Group 3 patients following administration of other PAH drugs showed no such improvements and had even decreased in patients receiving treatment resulting in the termination of those studies. In fact, the INCREASE study protocol itself included FVC and exacerbations of underlying lung disease as safety endpoints only.

1239. The significant skepticism in the field revolved around physicians' skepticism that the method of improving exercise capacity in PH-ILD patients using inhaled treprostinil—the indication that Tyvaso® has received approval for—would work. This product is the claimed invention.

**d) Failure of others**

1240. Numerous other clinical trials investigated treating a PH-ILD patient and/or other Group III PH patients using a drug approved to treat PAH. In fact, some attempts to treat these patients using drugs approved to treat PAH led to worse clinical outcomes. The repeated and consistent failure of others to develop a safe and effective treatment for PH-ILD demonstrates the complexity of the problem the inventors solved.

1241. The prior art did not identify options or solutions for improving exercise capacity in PH-ILD patients, nor the unique problems associated with administration of inhaled Treprostinil to PH-ILD patients.

1242. Drug manufacturers often persevere through repeated failures in a competitive drug race to develop a drug with positive results.

1243. Some physicians continued to prescribe Tyvaso to PH patients despite being aware of these failed studies. However these physicians carefully limited their Tyvaso® prescriptions to these severely ill patients with severe PH (rather than broadening their prescriptions to the full scope of PH-ILD patients) because of these failed studies and an absence of positive RCTs showing that treprostinil—or any other PAH drugs—worked in Group 3 PH patients.

1244. UTC's goals and the goals of the sponsors of the failed clinical trials were aligned: to discover a PAH drug that was both safe and effective to treat PH-ILD patients (or a subset of PH-ILD patients). The failed clinical trials (including RISE-IIP) would inform a POSA would expect in using inhaled treprostinil in a PH-ILD patient.

1245. UTC's optimism does not negate the failure of others. UTC's decision to invest in the INCREASE study and its optimism does not diminish the difficulty of achieving success where others had consistently failed to develop safe and effective treatment for PH-ILD.

1246. The failed studies would impact the practices of physicians as they would naturally

consider them in their risk/benefit analysis when determining whether it made sense to administer Tyvaso to those out of proportion patients with severe PH.

1247. There is a nexus between the claimed invention and the failure of others. Other studies repeatedly failed to solve the very problem UTC has claimed.

**e) The Results Claimed in the '327 Patent are Unexpected**

1248. A POSA would not expect that the claimed methods of improving exercise capacity in a PH-ILD patient through the administration of inhaled treprostinil (a previously approved PAH drug) would be successful, even in view of the prior art.

1249. A POSA would not expect that the claimed methods would result in increased 6MWD, reduced plasma concentration of NT-proBNP, and reduced clinical worsening events in PH-ILD patients.

1250. A POSA would not expect that that the claimed methods would result in reductions in exacerbations and improvements in FVC, among other claimed inventions.

1251. A POSA would not expect reductions in exacerbations, reductions in clinical worsening events, and improvements in FVC. As discussed in this section and above, it was unexpected that the administration of inhaled Treprostinil to PH-ILD patients would achieve these results.

1252. Previous attempts to use PAH treatments to treat PH-ILD failed.

1253. A POSA would be concerned that a PAH treatment could not safely and effectively treat a PH-ILD patient.

1254. The outcome of a large clinical trial like INCREASE is uncertain until the results are known—clinical trials exist to test hypotheses.

1255. The results of INCREASE were particularly uncertain given that every prior placebo-controlled trial in Group 3 PH had failed.

1256. No prior art asserted by Liquidia insufficient to support any expectation that the claimed methods would result in, for example, improved exercise capacity.

1257. Any anecdotal statement from physicians treating PH-ILD patients with inhaled Treprostinil who claimed those patients saw improvement is insufficient to support an expectation of success, especially given the failures of prior trials in Group 3 PH.

1258. The inventors had doubts that the INCREASE clinical trial would be successful until the study was unblinded.

1259. A POSA would not expect the results of the INCREASE based on the disclosures of the '793 Patent. Specifically, the '793 patent does not disclose or suggest a method of improving exercise capacity in a PH patient, let alone a PH-ILD patient.

1260. A POSA would not have expected the results of the INCREASE study based on a knowledge of Saggar 2014.

1261. For example, Saggar 2014 disclosed a study containing only 15 subjects that lacked a Placebo arm. The study tested the “sickest of the sick” and did not use inhaled Treprostinil, which would not lead a POSA to expect the results of INCREASE.

1262. Saggar 2014 did not measure critical endpoints and the reference itself admitted that it was “only hypothesis generating.”

1263. A POSA would not have expected the results of the INCREASE study based on their knowledge of Agarwal 2015.

1264. Agarwal 2015 discloses another small scale study that was not limited to PH-ILD patients. The study lacked a control arm and overall would not lead a POSA to expect the results of INCREASE.

1265. Agarwal 2015 only measured the effects of Treprostinil through 16 weeks. A POSA

could not infer from a 16 week data point what the effects would be after 6 months of treatment.

1266. Both the inventors and Agarwal 2015 itself indicate that the reference is only hypothesis generating and that a clinical trial would be necessary.

1267. A POSA would not have expected the results of the INCREASE study based on their knowledge of Faria-Urbina 2018.

1268. For example, Faria-Urbina 2018 is a report detailing a single-center retrospective report conducted on 22 patients with Group 3 PH. This report was not limited to patients with PH-ILD and did not contain a control group, which is critical to assess whether exacerbations were actually reduced, let alone to statistically significant levels. Faria-Urbina 2018 also focuses on the results at 3 months, but says nothing about the results at 8 weeks. A POSA cannot assume that a result present at 3 months would also present at 8 weeks.

1269. The inventors testified that Faria-Urbina 2018 had limitations and explained that the reference was only hypothesis generating.

1270. [REDACTED]

[REDACTED]

[REDACTED].

1271. Members on the INCREASE steering committee had doubts that INCREASE would yield the results that it did.

1272. The results of the INCREASE trial have a nexus to the asserted claims because the asserted claims claim the results of the INCREASE trial.

**f) The Claims of the '327 Patent have Demonstrated Remarkable Commercial success**

1273. Inhaled Treprostinil has achieved remarkable commercial and clinical success across the industry.

1274. There were no approved treatments for PH-ILD prior to the approval of Tyvaso's PH-ILD indication.

1275. UTC relied on the results of the INCREASE clinical trial to obtain approval for the PH-ILD indication.

1276. Tyvaso and Tyvaso DPI have been widely prescribed to improve exercise capacity in PH-ILD patients, since it received FDA approval for this indication in May 2022. Due to the lack of treatments in the PH-ILD space, physicians were quick to begin prescribing these drugs for the PH-ILD indication.

1277. The effect of the addition of the PH-ILD indication is apparent in the Tyvaso product's revenue and patient numbers after the change embodied in the claims in the '327 patent (i.e., the addition of the PH-ILD indication). As an example of this phenomenon is that Tyvaso products have generated significant revenues in recent years since the PH-ILD indication was added in April 2021.

1278. A company like UTC's business decisions (including the decision to innovate) can be driven by performing a cost-benefit analysis. That analysis will consider the expected revenues relative to the costs. Research and development is inherently risky and expensive thus when pharmaceutical companies anticipate high profits from an investment, they invest more in research and development and produce more new drugs.

1279. Despite the presence of UTC's patents, at least one company, Liquidia, went ahead and developed a product that would compete with Tyvaso and Tyvaso DPI which are covered by UTC's patents. This leads to the inference that Liquidia was not discouraged by UTC's patents and decided to engage in the costly affair of developing YUTREPIA anyway.

1280. The '793 Patent is not a blocking patent because it has not hindered incentives to

third parties potentially developing and commercializing a product with the innovation claimed in the '327 Patent.

1281. There was significant economic incentive to develop a treatment that was FDA approved to safely and effectively treat PH-ILD.

1282. Dr. Selck considered the testimony of Dr. Nathan that a physician would review the label of a drug and the underlying clinical study data prior to prescribing the drug, especially for an indication not listed on the label. Thus Dr. Selck considered the alleged prior use of Tyvaso to treat PH-ILD.

1283. Dr. Selck considered that the FDA approval allowed UTC engage in marketing campaigns to educate physicians regarding the safety and effectiveness of Tyvaso and Tyvaso DPI to treat PH-ILD.

1284. Physicians prescribe Tyvaso and Tyvaso DPI to PH-ILD patients to obtain the benefits demonstrated in the INCREASE study.

1285. The Tyvaso franchise earned net revenues of approximately \$607.5 million in 2021 (for only nebulized Tyvaso), \$873.0 million in 2022, \$1.23 billion in 2023, and \$1.20 billion through the first three quarters of 2024.

1286. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] ents.

1287. [REDACTED]

[REDACTED]

[REDACTED]

1288. [REDACTED]

[REDACTED]

[REDACTED]

1289. This is also evidenced by public statements UTC has made including the statement made by UTC's COO Michael Benkowitz: "We [] continued to increase the breadth and depth of the Tyvaso prescriber base. Since the PH-ILD launch in 2021, we have now doubled the number of Tyvaso prescribers."

1290. The growth in prescriptions and revenues for the Tyvaso products since the addition of the PH-ILD indication has been driven at least in part by increased prescriptions for PH-ILD.

1291. Mr. Kidder does no analysis to connect the partial Medicare coverage to make Tyvaso and the associated devices more affordable to certain patients to the commercial success of Tyvaso for the PH-ILD indication. If anything, these discounts would decrease the profits UTC obtains on the market for its drugs.

1292. The regression analysis performed by Mr. Kidder does not offer any new information and muddies the waters as to what caused the commercial success.

1293. UTC, like any pharmaceutical company made expenditures to educate physicians about the results of INCREASE. In so doing, UTC made attempts to assure physicians that



INCREASE demonstrated that Tyvaso could safely and effectively treat PH-ILD.

1294. The significant clinical success of Tyvaso following its approval for administration to PH-ILD patients is tied to the claims of the '327 Patent.

1295. The existence of the '793 patent does not negate nexus. The '793 patent does not disclose numerous limitations that are disclosed by the '327 patent. A salient example is that the '793 patent does not disclose an increase in exercise capacity, which is disclosed in the '327 patent.

1296. Mr. Kidder did not consider the relevant *Acorda* factors that bear on whether a potentially “blocking” patent actually deterred a competitor from pursuing a competing product. Mr. Kidder did not consider the costliness of the project, the risk of research failure, or the size of the market opportunity, and how that might or might not deter a potential competitor from bringing a competing product to market.

1297. Regulatory exclusivity, taken alone, is not a guarantee that the drug will be commercially successful.

**g) Liquidia Copied the Claims of the '327 Patent**

1298. Liquidia relied on the invention claimed in the '327 Patent in its proposed 505(b)(2) product and the Yutrepia Label. In fact, Liquidia copied many sections from the Tyvaso Label into the Yutrepia Label nearly verbatim.

1299. Liquidia has not submitted any of its own data to the FDA reflecting the use of Yutrepia in PH-ILD patients, instead, Liquidia relied entirely on UTC's data from the INCREASE study in order to obtain a PH-ILD indication for Yutrepia.

1300. Liquidia's Yutrepia label directly cites the INCREASE study and contains an identical PH-ILD indication as compared to Tyvaso.

1301. Liquidia began considering a PH-ILD indication since at least 2020 when top line results from INCREASE were released. Nathan Opening Rep. In fact, at Liquidia's LIQ861

Steering Committee meeting, [REDACTED]. Nevertheless, Liquidia did not actually begin studying Yutrepia in PH-ILD until December 2024 when it initiated its ASCENT study. Liquidia chose to reference and rely directly on UTC's INCREASE study data to get its own PH-ILD indication.

1302. Liquidia's CMO, Dr. Rajeev Saggar, reached out to the FDA for advice on [REDACTED]. Liquidia performed no studies beyond comparative studies, instead relying on the results of the INCREASE study to support the PH-ILD indication for Yutrepia. Indeed, Dr. Rajeev Saggar solicited this advice *so that* no additional studies would be required.

1303. Dr. Saggar believed that Yutrepia would be just as effective as Tyvaso for patients with PH-ILD.

1304. The FDA responded to Liquidia's request to add the PH-ILD indication to its Yutrepia product by stating that Liquidia would not need to conduct any additional clinical or non-clinical studies in view of Liquidia's reliance on the INCREASE study.

1305. Because both Tyvaso and Yutrepia rely on the INCREASE study and the INCREASE study serves as the basis for the claimed invention of the '327 patent.

1306. Liquidia has copied the invention claimed in the '327 patent which aligns precisely with the methods of administration used in the INCREASE study.

**h) Praise**

1307. Tyvaso received tremendous positive recognition by academics and practitioners alike following INCREASE. This positive recognition from academics and industry professionals alike highlights the unique and non-obvious nature of the claimed invention of the '327 patent, as it demonstrates that academics and practitioners in the field acknowledged the substantial value and innovation of the method of administration claimed in the '327 patent.

1308. Examples of key opinion leaders who have praised the results of the INCREASE include Dr. Shelley Shapiro and Dr. Waxman. Both lauded the groundbreaking nature of a drug approved to treat PH-ILD.

1309. Imitation is the highest form of flattery and competitors like Liquidia have institute similar PH-ILD trials to study the ability of their own inhaled Treprostinil drugs to improve exercise capacity.

1310. Dr. Rajeev Saggar stated that the INCREASE study was a “bold move” and “nothing short of transformative.”

1311. The academic community praise and industry praise was directed to the successful INCREASE study which served as the basis for and aligns directly with the claimed invention, meaning that the praise Tyvaso received is connected to the claims of the '327 Patent.

**F. Claims 9 and 10 of the '327 Patent Have Sufficient Written Description**

1312. A POSA reading the disclosures of the '327 patent would have understood that the inventors were in possession of the inventions described in claims 9 and 10 of the '327 patent.

1313. A POSA would have understood that the FVC data reported in Examples 1 and 3 of the '327 patent are substantively the same as the FVC data reported in Example 1 of the '810 Provisional and that the inventors were in possession of claims 9 and 10 of the '327 patent for the same reasons the inventors were in possession of claims 9 and 10 of the '327 patent with respect to the priority analysis regarding the '810 Provisional.

**1. Claim 9**

1314. A POSA reading the '327 patent would have understood that the inventors were in possession of claim 9 of the '327 patent.

1315. As described above, a POSA reading the '327 patent would have understood that the inventors were in possession of claim 1 of the '327 patent

1316. A POSA reading the '327 patent would have understood that the administration of inhaled treprostinil to PH-ILD patients disclosed therein resulted in all patient populations exhibiting a statistically significant improvement in percent predicted FVC after 8 and 16 weeks of treatment.

1317. A POSA reading the '327 patent would have understood that the administration of inhaled treprostinil to PH-ILD patients disclosed therein resulted in the PH-IIP and PH-IPF patient populations exhibiting a statistically significant improvement in absolute FVC after 16 weeks of treatment. These subpopulations represent approximately 43% and 27% of the study patient population with reported FVC results, respectively, which a POSA would understand to be consistent with IIP being the largest general category of ILD and IPF in turn being the largest subset of IIP.

1318. A POSA would understand that in the context of the clinical trial described in Examples 1 and 3 of the '327 patent, percent predicted FVC would be a preferable way to express the FVC data because it normalizes the change in FVC for every individual patient's underlying physiology.

1319. A POSA trying to determine whether the inventors possessed a treatment method that would produce statistically significant improvement in FVC as required by claim 9 of the '327 patent, would primarily look to the percent predicted expression of FVC data, not the presentation of that same data in terms of absolute volume.

1320. To the extent a statistically significant improvement in both absolute FVC and percent predicted FVC is required to demonstrate that the inventors were in possession of the invention described in claim 9 of the '327 patent, a POSA would understand that the '327 patent clearly identifies which particular embodiments of claim 9 of the '327 patent are operable—i.e.,

the IIP and IPF subpopulations at week 16—and provides supporting data for these embodiments. In this scenario, a lack of statistically significant improvement in absolute FVC for other embodiments of the claim would not cause a POSA to conclude that the inventors lacked possession of the method described in claim 9 of the '327 patent.

1321. A POSA reading the '327 patent would have understood that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent would result in a statistically significant improvement of FVC after 8, 12, or 16 weeks.

## **2. Claim 10**

1322. A POSA reading the '327 patent would have understood that the inventors were in possession of claim 10 of the '327 patent.

1323. As described above, a POSA reading the '327 patent would have understood that the inventors were in possession of claims 1 and 9 of the '327 patent.

1324. A POSA reading claim 10 of the '327 patent would understand claim 10 of the '327 patent to require a 20 mL improvement in absolute FVC after 8 weeks, 12 weeks, or 16 weeks of treatment, but would not understand the claim to require that this 20 mL improvement be statistically significant.

1325. As discussed above, Examples 1 and 3 of the '327 patent disclosed that across all patient populations, PH-ILD patients administered inhaled treprostinil exhibited an improvement in their absolute FVC after both 8 and 16 weeks as compared to placebo. Further, these improvements in absolute FVC were statistically significant at the 16 week time point for the PH-IIP and PH-IPF populations.

1326. To the extent a statistically significant improvement in absolute FVC is required to demonstrate that the inventors were in possession of the invention described in claim 10 of the '327 patent, a POSA would understand that the '327 patent clearly identifies which particular

embodiments of claim 10 of the '327 patent are operable—i.e., the IIP and IPF subpopulations at week 16—and provides supporting data for these embodiments. In this scenario, a lack of statistically significant improvement in absolute FVC for other embodiments of the claim would not cause a POSA to conclude that the inventors lacked possession of the method described in claim 10 of the '327 patent.

1327. A POSA reading the '327 patent would have understood that the administration of inhaled treprostinil to PH-ILD patients consistent with the method of claim 1 of the '327 patent would result in both (i) a statistically significant improvement in FVC; and (ii) an improvement in absolute FVC of at least 20 mL after 8, 12, or 16 weeks.

## **VI. FACTS PERTAINING TO THE ENFORCEABILITY OF THE '327 PATENT**

### **A. Background**

1328. Stephen Maebius, Esq., and Shaun Snader, Esq., were involved in the prosecution of the '061 application, which issued as the '327 Patent.

1329. Mr. Maebius is currently a Partner at the firm Foley & Lardner LLP, where he has practiced law continuously since his graduation from law school in 1994. Mr. Maebius's principal practice area is patent prosecution and IP portfolio management for life sciences clients.

1330. Mr. Maebius first began prosecuting patents before the USPTO in 1991 as a registered Patent Agent.

1331. Mr. Maebius has been engaged as outside patent counsel for UTC since its inception.

1332. During his three decades prosecuting patents before the USPTO, no court has ever found that Mr. Maebius committed inequitable conduct.

1333. Mr. Snader currently serves as UTC's Vice President and Associate General Counsel, Intellectual Property. Mr. Snader has been employed at UTC since 2015. Mr. Snader's

duties at UTC include managing patent prosecution activities and supervising outside counsel in that respect.

1334. [REDACTED]

[REDACTED]

[REDACTED]

1335. In the course of his two decades practicing law, no court has ever found that Mr. Snader committed inequitable conduct.

**B. No Inequitable Conduct**

1336. Messrs. Maebius and Snader satisfied their full duty of disclosure to the USPTO during the prosecution of the '327 patent.

1337. Messrs. Maebius and Snader disclosed all material references and information to the USPTO during the prosecution of the '327 patent.

1338. Messrs. Maebius and Snader did not act with the intent to deceive the examiner during the prosecution of the '327 patent.

1339. Messrs. Maebius and Snader did not engage in inequitable conduct during the prosecution of the application that would become the '327 Patent.

**1. No Material Information Was Withheld From the Examiner**

1340. Messrs. Maebius and Snader withheld no material information from the Examiner during prosecution of the '061 application.

1341. Messrs. Maebius and Snader disclosed U.S. Pat. No. 10,716,793 (the "'793 Patent") to the USPTO during prosecution of the '061 application.

1342. Messrs. Maebius and Snader disclosed Liquidia's '793 IPR petition to the patent office during prosecution of the '061 application.

1343. The Examiner who reviewed the '061 application understood that the term

“pulmonary hypertension” as recited claim 1 of the ’793 Patent included all five groups of pulmonary hypertension, and, in particular, PH-ILD (a type of group 3 PH).

1344. The Examiner who reviewed the ’061 application understood that Claim 1 of the ’793 Patent would encompass using inhaled treprostinil to improve the hemodynamics of a patient with pulmonary hypertension, including a patient with PH-ILD.

1345. The ’793 Patent is cumulative of every document Defendant’s allege was intentionally from the USPTO during prosecution of the application that would become the ’327 Patent. These allegedly withheld documents include (1) the Court’s opinion in the previous District Court litigation, (2) Dr. Hill’s district court trial testimony, (3) the Federal Circuit’s affirmance of the District Court’s opinion, (4) UTC’s Patent Owner Response submitted in the ’793 IPR, (5) the ’793 IPR declaration of Dr. Waxman, (6) the PTAB’s Final Written Decision, and (7) the Federal Circuit’s opinion affirming the PTAB’s Final Written Decision (numbers (1)-(3) collectively referred to as “the District Court Documents” and numbers (4)-(7) collectively referred to as “the ’793 IPR Documents”).

1346. Defendants allege that the material information found in the District Court Documents is how the ’793 patent’s claims describe the use of treprostinil in connection with PH-ILD. This allegedly material information was already before the examiner from Agarwal 2015, the ’793 patent itself, and the three documents the examiner cited in their March 6, 2023 rejection: WO 2008/098196, WO 2016/205202, and WO 2015/138423.

1347. The Federal Court’s affirmance relied exclusively on the ’793 patent specification’s text to interpret the claims of the ’793 patent because it indicated that ““the specification does not limit the scope of ‘pulmonary hypertension’ to any particular subset of pulmonary hypertension patients and referred to both ‘precapillary pulmonary hypertension’ and ‘pulmonary hypertension,’



which, as the court found, demonstrates that the inventors view precapillary PH only as a subset of the broadly claimed ‘pulmonary hypertension.’

1348. The Examiner considered WO 2008/098196, WO 2016/205202, and WO 2015/138423 during prosecution of the ’061 application.

1349. Each of WO 2008/098196, WO 2016/205202, and WO 2015/138423 disclose the use of treprostinil to improve the hemodynamics of patients suffering from Group 3 pulmonary hypertension, including patients with PH-ILD.

1350. In rejecting the ’061 application, the Examiner cited to WO 2008/098196, WO 2016/205202, and WO 2015/138423 for the proposition that the prior art taught inhaled treprostinil could be used treat patients with pulmonary hypertension due to chronic lung disease, which would include patients with PH-ILD.

1351. WO 2008/098196, WO 2016/205202, and WO 2015/138423 are cumulative with the documents Liquidia alleges were withheld from the USPTO during prosecution of the ’061 application.

1352. Improvement in hemodynamics is different from improvement in exercise capacity, and the two measures are not necessarily correlated.

1353. The ’793 IPR petition is cumulative with the ’793 IPR Documents that Liquidia alleges Messrs. Snader and Maebius withheld from the Examiner during prosecution of the ’061 application.

1354. Defendants allege that the material information found in the ’793 IPR Documents is how the ’793 patent’s claims describe the use of treprostinil in connection with PH-ILD. This allegedly material information was already before the examiner from Agarwal 2015, the ’793 patent itself, and the three documents the examiner cited in their March 6, 2023 rejection: WO

2008/098196, WO 2016/205202, and WO 2015/138423.

1355. The '793 patent "cover[s] methods of treating PH-ILD," and nothing in the '793 IPR disclosed any information that varies from the scope of analysis that the examiner would have conducted. The '793 IPR did not and does not change the scope of the '793 patent.

1356. The Final Written Decision of the '793 IPR is cumulative of the '793 IPR petition itself. Because the existence of the '793 IPR was made known to the examiner, the Final Written Decision of the '793 patent is substantively duplicative of documents and information in the '793 IPR and thus the information before the examiner during the prosecution of the '327 patent.

## **2. No Intent to Deceive the Examiner**

1357. Messrs. Snader and Maebius did not intend to deceive the Examiner during prosecution of the '061 application.

1358. Messrs. Snader and Maebius did not believe that the Examiner misunderstood the disclosure of the '793 Patent.

1359. Messrs. Snader and Maebius believed that the '793 Patent was cumulative with the documents Liquidia has alleged were intentionally withheld from the Examiner during prosecution of the '061 application.

1360. Messrs. Snader and Maebius did not intentionally fail to submit or notify the Examiner about the allegedly withheld references identified as the District Court Documents and the '793 IPR Documents above. *See supra* VI.B.1.

# EXHIBIT 3

**THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

UNITED THERAPEUTICS  
CORPORATION,

*Plaintiff,*

v.

LIQUIDIA TECHNOLOGIES, INC.,

*Defendant.*

C.A. No. 1:23-cv-00975-RGA



**DEFENDANT’S STATEMENT OF CONTESTED FACTS**

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## **DEFENDANT’S STATEMENT OF CONTESTED FACTS**

Defendant Liquidia Technologies, Inc. (“Liquidia”) provides the following statement of contested facts that remain to be litigated at trial. This statement is based on the parties’ pleadings, documentary and testimony evidence, and Liquidia’s current understanding of Plaintiff’s claims and defenses and the Court’s rulings to date. Pursuant to Fed. R. Civ. P. 26(a)(3) and agreement of the parties, Liquidia submits the attached statement of contested facts. Liquidia reserves the right to revise, amend, supplement, or modify its statement of contested facts based upon any pretrial rulings by the Court and/or to address any additional issues, arguments, evidence or other developments in the case, including edits to the draft pretrial order, any meet and confers or other negotiations between the parties, pending and anticipated motions, and similar developments. Liquidia further reserves the right to supplement this statement to rebut or otherwise address the contested facts identified by Plaintiff. Should the Court determine that any issue identified in this statement is more properly considered an issue of law, it shall be so considered and Liquidia incorporates it by reference into its Statement of Issues of Law. Liquidia contends that the issues of fact (or mixed questions of fact and law) that remain to be litigated at trial and decided by the Court are as follows:

### **I. BACKGROUND**

#### **A. Nature and Stage of the Proceedings**

1. Defendant Liquidia submitted New Drug Application No. 213005 under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act (“Liquidia’s NDA”) to the United States Food and Drug Administration (“FDA”) seeking approval to engage in the commercial manufacture, use and/or sale of YUTREPIA (treprostinil) inhalation powder with an indication for the treatment of pulmonary arterial hypertension (“PAH”). Liquidia obtained tentative approval

to market YUTREPIA, a dry powder formulation of treprostinil, in the United States on November 4, 2021.

2. On March 31, 2021, Tyvaso®, the listed drug for Liquidia’s NDA No. 213005, added an indication for the treatment of pulmonary hypertension associated with interstitial lung disease (“PH-ILD”). On July 24, 2023 Liquidia submitted an amendment to NDA No. 213005 to the FDA seeking to add the PH-ILD indication to its prescribing information, thereby aligning the labeling with that of the application’s listed drug. Liquidia sent Plaintiff United Therapeutics Corporation (“UTC”) a paragraph IV certification upon filing that NDA.

3. UTC in turn filed this suit, alleging that Liquidia infringed U.S. Patent No. 10,716,793 (the “’793 patent”). (D.I. 1.) UTC filed an amended complaint adding allegations that Liquidia infringed U.S. Patent No. 11,826,327 (the “’327 patent”) after the ’327 patent issued on November 28, 2023. (D.I. 8.) Liquidia filed a motion to dismiss the allegations of infringement of the ’793 patent from the case because the Federal Circuit affirmed the invalidity of the ’793 patent on December 20, 2023. (D.I. 13.) The parties entered a partial dismissal stipulation, leaving only the ’327 patent at issue. (D.I. 17.) In particular, UTC alleges infringement of claims 1-11 and 14-19 of the ’327 patent. At trial, Liquidia plans to show that these claims are invalid and not infringed based on the facts presented below.

## **B. The Parties’ Products at Issue**

4. UTC has two products relevant to this trial. On July 30, 2009, the FDA approved NDA 22387 for Tyvaso®, a treprostinil inhalation solution administered through use of an ultrasonic pulsed nebulizer, for “the treatment of pulmonary arterial hypertension [PAH] (WHO Group 1)[.]” (DTX0357, 2009 Tyvaso® Label, UTC\_PH-ILD\_010693.) In 2021, the FDA additionally approved Tyvaso® “for the treatment of pulmonary hypertension associated with

interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (DTX0360, 2021 Tyvaso® Label, UTC\_PH-ILD\_010744.) In 2022, the FDA approved NDA 22387 for Tyvaso DPI®, a treprostinil dry powder administered through the use of a dry powder inhaler, for both “the treatment of pulmonary arterial hypertension ([PAH,] WHO Group 1).” and “for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability[.]” (DTX0358, Tyvaso DPI® 2022 Label, UTC\_PH-ILD\_010709; DTX0630, 2022 FDA Approval of Tyvaso DPI® Press Release, UTC\_PH-ILD\_005419).

5. Liquidia’s YUTREPIA (also known as LIQ861) is a dry powder formulation of treprostinil administered by oral inhalation using a dry powder inhaler. (See DTX0118, 2024 YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126020.) YUTREPIA is not a “generic” product or “copy” of Tyvaso®. While YUTREPIA uses treprostinil as its active pharmaceutical ingredient, its formulation, dosage form, and route of administration are different from Tyvaso®. In particular, patients administer YUTREPIA using the Plastiaple RS00 Model 8 dry powder inhaler. (DTX0045, N. Hill, et al., INSPIRE: Safety and tolerability of inhaled Yutrepia (treprostinil) in pulmonary arterial hypertension (PAH), *Pulmonary Circulation* 12: e12119 (2022) (LIQ\_PH-ILD\_00001670) (“Hill 2022”) at LIQ\_PH-ILD\_00001671.) YUTREPIA’s dry powder inhaler is comprised of a mouthpiece, a capsule chamber, an air channel, and two push buttons used to puncture the capsule containing the treprostinil dry powder. (DTX0118, 2024 YUTREPIA Label at LIQ\_PH-ILD\_00126034.) The YUTREPIA dry powder inhaler is used by placing a YUTREPIA capsule in the capsule chamber, using the push buttons to break the capsule, and inhaling the released treprostinil through the air channel and mouthpiece in two breaths. The YUTREPIA dry powder inhaler does not include any electronic machinery; and it does not itself generate any energy or power to expel powder from the device. The YUTREPIA

dry powder inhaler is also a low-resistance inhalation device in that it only requires the patient to exert a low level of force to inhale the drug properly, allowing patients with a wide range of lung capacities to use the device. It has a different formulation, dosage form, and method of administration than Tyvaso®. For example, Tyvaso® is a liquid formulation delivered via a nebulizer. Yutrepia® is a powder formulation delivered via dry powder inhaler.

6. Liquidia first sought approval for YUTREPIA for treatment of Group 1 PAH. On November 5, 2021 before Tyvaso DPI® was approved, the FDA granted tentative approval of YUTREPIA. The FDA tentatively approved NDA 213005 for YUTREPIA on November 4, 2021. (DTX0677, LIQ\_PH-ILD\_00015477 (Nov. 2021 Tentative Approval).) In 2022, Liquidia amended its NDA to add an indication for treating “pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (DTX0118, LIQ\_PH-ILD\_00126017 (“YUTREPIA Label”).) On August 16, 2024, Liquidia received tentative approval for YUTREPIA to improve exercise ability in PH-ILD patients. (*Id.*)

7. The YUTREPIA label references the INCREASE study, UTC’s clinical trial that evaluated the safety and efficacy of inhaled treprostinil in patients with PH-ILD, in Section 14.2. (*Id.* at LIQ\_PH-ILD\_00126031.) The primary endpoint for INCREASE, as reported in the label, was the change in 6-Minute Walk Distance (“6MWD”) from baseline to Week 16. (*Id.*) As implied by the name, 6MWD is an objective endpoint measuring the distance in meters a patient can walk in six minutes.

8. While the YUTREPIA label provides a summary of certain INCREASE study results, it provides only a limited subset of the data from the study. Specifically, the YUTREPIA label only reports data regarding the change in 6MWD (primary endpoint) and the time to clinical worsening (exploratory endpoint) due to PH-ILD. Importantly, the YUTREPIA label does *not*

report any data on other endpoints from the INCREASE study, such as: changes in forced vital capacity (“FVC”), changes in NT-proBNP levels (a biomarker for heart strain), changes in exacerbations, or any other exploratory endpoints. (DTX0118, YUTREPIA Label at LIQ\_PH-ILD\_00126031-033.)

9. The full results of the INCREASE study and INCREASE-related publications are not incorporated by reference in any way into the YUTREPIA label. Healthcare providers are not instructed or required by the label to review the full INCREASE study data or any associated publications to understand the drug’s approved indications, safety, or proper use and administration. (Anticipated testimony of Dr. Channick.) Furthermore, the YUTREPIA label expressly provides that “[b]ecause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug *cannot be directly compared to rates in the clinical trials of another drug*[.]” (*Id.* at LIQ\_PH-ILD\_00126023 (emphasis added).) This caveat is noteworthy given the extensive differences between YUTREPIA and Tyvaso®. (Anticipated testimony of Dr. Channick.)

### C. Defendant Liquidia’s Experts

10. Dr. Richard Channick is an expert witness proffered by Liquidia. Dr. Channick is a medical doctor with more than 35 years of experience treating pulmonary diseases, including pulmonary hypertension. (Anticipated testimony of Dr. Channick.) Dr. Channick has treated thousands of patients with pulmonary hypertension, including PH-ILD, and treats more than 100 patients with PH-ILD every year. (*Id.*) Dr. Channick has published over 150 original articles in peer-reviewed journals, including many on PH. (*Id.*) Dr. Channick has also served as the co-chair of the task force of the 7<sup>th</sup> World Health Symposium in Pulmonary Hypertension, which devised the criteria for diagnosing PH-ILD. (*Id.*) Dr. Channick currently serves as a Pulmonary and

Critical Care Division of the David Geffen School of Medicine at UCLA and an Attending Physician for Pulmonary and Critical Care at the UCLA Medical Center. He also serves as the Saul Brandman Endowed Chair in Pulmonary Arterial Hypertension at UCLA Medical Center. Dr. Channick will testify about the state of the art for methods of treating pulmonary hypertension associated with interstitial lung disease, from the clinician's perspective, as of April 17, 2020. Dr. Channick will also testify on the priority date, invalidity, and non-infringement of the '327 patent. (*Id.*)

11. Dr. Nicholas Hill is an expert witness proffered by Liquidia. Dr. Hill is a medical doctor with more than 43 years of experience treating pulmonary disease, including pulmonary hypertension. (Anticipated testimony of Dr. Hill.) He has treated hundreds of patients with pulmonary hypertension, including PAH and PH-ILD, and has prescribed inhaled prostacyclin analogues, including treprostinil (Tyvaso®) and iloprost, to many dozens of these patients. (*Id.*) Dr. Hill has participated in the conduct and oversight of over two dozen clinical trials evaluating treatments for pulmonary hypertension, including treatments for Groups 1 and 3 PH with inhaled therapies. Notably, he participated in a multi-center trial on the effects on PAH of the addition of inhaled treprostinil to sildenafil or bosentan and is currently an investigator in the two TETON trials, both UTC-sponsored Phase III studies evaluating safety and efficacy of inhaled treprostinil in patients with IPF and progressive pulmonary hypertension (PPH), respectively. (*Id.*) Dr. Hill has also consulted for many companies regarding the treatment of pulmonary hypertension. (*Id.*) Dr. Hill was Chief of the Division of Pulmonary, Critical Care, and Sleep at Tufts Medical Center through 2023 and recently stepped down as division chief. He currently serves as the Director of Pulmonary Research. He is also a Professor of Medicine at Tufts University School of Medicine where he researches pulmonary vascular biology, disease, and treatment. Dr. Hill will testify about

the state of the art for methods of treating PH-ILD as of April 17, 2020, and will specifically testify on improper inventorship, invalidity of the '327 patent based on prior public use and prior public sale, and the unenforceability of the '327 patent due to inequitable conduct.

12. Dr. Stephan Ogenstad is an expert witness proffered by Liquidia. He holds a B.Sc. in Mathematics, Statistics, and Computing from Stockholm University and received a Ph.D. in statistics from the same institution in 1982. (Anticipated testimony of Dr. Ogenstad.) Dr. Ogenstad has developed 650+ study protocols and statistical analysis plans and conducted statistical analysis for NDA/Biologics License Application ("BLA")/Investigational New Drug ("IND") submissions. (*Id.*) He has been the lead biostatistician preparing more than 40 original FDA submissions, as full 505(b)(1) NDAs, interactions with the FDA, and study designs and analyses. (*Id.*) For the past decade, Dr. Ogenstad has been a biostatistician with CardioMEMS and MiRus, where he has been deeply involved in statistical analysis and data modeling for medical device trials and research. He has also served as an Adjunct Faculty Member and Professor of Biostatistics at Georgia Southern University for the last 12 years. Since 2006, Dr. Ogenstad has been the President of Statogen Consulting LLC, where he consults with companies in the pharmaceutical, biotechnology, and medical device industries to help bring new products to market. (*Id.*) Dr. Ogenstad will testify about (a) the process of clinical drug development, (b) the use of statistical analysis in the interpretation of clinical data; (c) the basis for a reasonable expectation that a clinical drug will succeed in treating certain diseases, and (d) the significance of clinical data from certain clinical trials discussed by Drs. Channick and Hill during their testimony.

13. Mr. Douglas Kidder is an expert witness proffered by Liquidia. Mr. Kidder holds a B.A. in Mathematics and English with Honors from Amherst College and a Master of Science from the University of California at Berkeley. (Anticipated testimony of Mr. Kidder.) He has



been performing business analyses and valuations for over 35 years and has been retained by companies to render expert opinions in the context of litigation to assist in licensing and evaluation of intellectual property that is not subject to litigation, and to develop and refine business strategies. (*Id.*) Mr. Kidder has co-authored seven published articles relating to intellectual property damages and has published multiple articles on business and valuation issues related to intellectual property. Mr. Kidder was also an Adjunct Professor in the Accounting Department at Golden Gate University. (*Id.*) Mr. Kidder is currently a Managing Partner with OSKR, LLC, a firm that provides expert services primarily in the area of area of damages calculations generally with a particular focus on intellectual property and antitrust matters. (*Id.*) Mr. Kidder will testify regarding the information in Dr. Selck's expert report and commercial success.

## **II. SCIENTIFIC BACKGROUND RELEVANT TO '327 PATENT**

### **A. Pulmonary Hypertension Generally**

14. Pulmonary hypertension, or PH, refers to abnormally high blood pressure in the lungs. (DTX0041, LIQ\_PH-ILD\_00001419.) Patients with PH have higher than normal pressure in the pulmonary arteries, meaning the right side of the heart has to work harder to pump blood to the lungs. As a result, patients with PH may experience shortness of breath, chest pain, lightheadedness, fatigue, fainting spells, and swelling in their extremities.

15. Typically, PH is diagnosed by measuring mean pulmonary arterial pressure ("mPAP") by right heart catheterization. In healthy individuals, the normal mPAP range is between 8–20 millimeters of mercury ("mmHg"). Patients with PH, however, exhibit mPAP levels greater than 25 mmHg. (DTX0356, G. Simonneau, et al., Haemodynamic definitions and updated clinical classification of pulmonary hypertension, *Eur. Respir. J.* 53: 1801913 (2019) (UTC\_PH-ILD\_010679) ("Simonneau 2019").) In 2018, the World Symposium on Pulmonary Hypertension lowered the upper limit of normal mPAP to 20 mmHg, with any pressure above that meeting the

definition for pulmonary hypertension. (*Id.* at UTC\_PH-ILD\_010679–80.) Mean arterial pressure is measured using a technique called right heart catheterization, where a thin tube is inserted into a vein (typically in the neck or arm) of the patient and directed to the right side of the heart. Using this technique, physicians can record or derive not only mPAP but also other measures, including pulmonary vascular resistance or “PVR” (a measure of how difficult it is for blood to flow through those vessels, with a higher number indicating more difficulty) and pulmonary arterial wedge pressure or “PAWP” (an estimate of the pressure in the left ventricle of the heart).

16. Pulmonary hypertension is not a single condition. Instead, pulmonary hypertension includes a range of conditions that are classified in five different groups depending on, amongst other factors, the underlying pathophysiology and clinical presentation. As of the filing date of the ‘327 patent” in April 2020, the five groups were as follows:

- **WHO Group 1:** Pulmonary arterial hypertension (“PAH”);
- **WHO Group 2:** PH due to left heart disease;
- **WHO Group 3:** PH due to lung diseases and/or hypoxia. This Group includes PH due to obstructive lung diseases like chronic obstructive pulmonary disease (“COPD”), restrictive lung diseases like interstitial lung disease (“ILD”) which includes combined pulmonary fibrosis and emphysema (“CPFE”), hypoxia, and developmental lung disorders;
- **WHO Group 4:** PH due to pulmonary artery obstructions. This group includes chronic thromboembolic PH;
- **WHO Group 5:** PH due to unclear and/or multifactorial mechanisms, including hematological disorders, systemic and metabolic disorders, and complex congenital heart disease.

(DTX0356, Simonneau 2019 at UTC\_PH-ILD\_010684 (Tbl. 2); DTX0056, G. Simonneau, et al., *Clinical Classification of Pulmonary Hypertension*, J. Am. Coll. Cardiol., 43(12):5S-12S (2004) (LIQ\_PH-ILD\_00002479) (“Simonneau 2004”), at LIQ\_PH-ILD\_00002480 (Tbl. 1).)

17. There is disease heterogeneity even within each of the five groups. Thus, patients may be classified as mixed—for example mixed Group 1 and Group 3 or mixed Group 1 and Group 2. In fact, the five group classification system is used primarily as an organization tool, but in reality, many patients do not fall neatly within a single group and instead exhibit characteristics of multiple groups. Notably, in a 2022 study of 1,193 patients describing the characteristics of the five PH groups, mixed etiology PH or PH involving more than one group was identified in 38.9% of patients. (Anticipated testimony of Drs. Channick/Hill; DTX0164, Anna R. Hemnes et al, *Clinical Characteristics and Transplant-Free Survival Across the Spectrum of Pulmonary Vascular Disease*, 80 J. Am. College Cardiology 697 (2022) at 705 (LIQ\_PH-ILD\_00148567).)

18. Pulmonary hypertension patients can also be grouped based on whether the etiology of their pulmonary hypertension is precapillary or postcapillary. Groups 1, 3, 4, as well as some forms of Group 5, most often manifest hemodynamic abnormalities characteristic of “precapillary pulmonary hypertension” while Group 2 (and some forms of Group 5) are generally referred to as “postcapillary pulmonary hypertension.” This is because Group 2 pulmonary hypertension is characterized by left-sided heart anomalies and deficiencies, and the left heart (*i.e.*, left ventricle, left atrium, and associated valves) is found **after** or downstream from the pulmonary capillaries in the cardiopulmonary circulation system. These left-sided heart issues generally relate to the inability of this side of the heart to sufficiently move blood from the pulmonary circulation into the systemic circulation. (Anticipated testimony of Drs. Channick/Hill.)

19. Precapillary pulmonary hypertension and postcapillary hypertension can be further differentiated in a clinical setting based on a hemodynamic parameter called PAWP. A patient with postcapillary pulmonary hypertension (Group 2 pulmonary hypertension and some forms of Group 5 pulmonary hypertension) has a PAWP of greater than 15 mmHg, while a patient with

Group 1, 3, 4, or 5 pulmonary hypertension has a PAWP of 15 mmHg or less. (DTX0356, Simonneau 2019 at UTC\_PH-ILD\_010682 (Table 1).) Groups 1, 3, 4, and 5, including PH-ILD, have other similar hemodynamic profiles ( $\text{mPAP} \geq 25$  mmHg,  $\text{PVR} \geq 3$  Wood Units), and thus, the 6th World Symposium on Pulmonary Hypertension task force proposed including a pulmonary vascular resistance of  $\geq 3$  Wood Units in the definition of all forms of pre-capillary hypertension associated with mPAP. (*Id.* at UTC\_PH-ILD\_010679–81.)

**B. Pulmonary Arterial Hypertension**

20. Pulmonary arterial hypertension, or PAH, is pre-capillary hypertension, which falls under WHO Group 1 PH. (DTX0169, Hill 2016 (LIQ\_PH-ILD\_00148671).)

21. Patients with PAH may suffer from persistent and progressive shortness of breath upon exertion, chest pain, fatigue, syncope (fainting), and dizziness. (*Id.* at LIQ\_PH-ILD\_00148678.) In advanced stages of the disease, patients may present with right ventricular heart failure, syncope upon exertion, peripheral edema (swelling/fluid build-up in the peripheral parts of the body such as the legs), and abdominal swelling. (*Id.*) Left untreated, patients in advanced stages of the disease may die. (*Id.* at LIQ\_PH-ILD\_00148675.)

22. The approved drugs for PAH mainly act on the blood vessels of the lungs to dilate those vessels (“vasodilation”) and decrease pressure. To induce vasodilation, the drugs utilize different molecular signaling pathways—the prostacyclin, nitric oxide, or endothelin pathways. (DTX0174, Marc Humbert et al, *Treatment of Pulmonary Arterial Hypertension*, 351 N. ENG. J. MED. 1425-436 (2004) (LIQ\_PH-ILD\_00148732) at LIQ\_PH-ILD\_00148734.)

**C. Pulmonary Hypertension Associated with Interstitial Lung Disease**

23. Pulmonary hypertension associated with interstitial lung disease, or PH-ILD, is pre-capillary pulmonary hypertension, which falls under Group 3 PH. (*See supra* paragraphs 18-19;

Anticipated testimony of Drs. Channick/Hill.) PH-ILD, as the name suggests, consists of both a PH component and an interstitial lung disease component. Interstitial lung disease or “ILD” refers to a heterogenous group of progressive lung disorders characterized by fibrosis (i.e., stiffening and scarring) of the lung tissue. (Anticipated testimony of Dr. Channick.) This thickening and scarring makes it more difficult for oxygen to pass from the alveoli to the blood in the vessels of the lungs.

24. Interstitial lung disease has a variety of associated causes and conditions including idiopathic interstitial pneumonia (“IIP”), chronic hypersensitivity pneumonitis, occupational lung disease, pulmonary fibrosis (“PF”); idiopathic pulmonary fibrosis (“IPF”), which is PF of an unknown cause; combined pulmonary fibrosis and emphysema (“CPFE”), and connective tissue disease (“CTD”). (Anticipated testimony of Dr. Channick.) Additional conditions that are also classified as interstitial lung disease including desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, silicosis, asbestosis, occupational lung disease, chronic hypersensitivity pneumonitis, idiopathic interstitial pneumonia (IIP), an autoimmune ILD, lymphangioleiomyomatosis (LAM), Langerhans cell histiocytosis (LCH), drug-associated ILD, vasculitis, granulomatosis, berylliosis, and systemic sclerosis-associated interstitial lung disease (SSc-ILD). (Anticipated testimony of Dr. Channick; DTX0001, (“327 patent”) at 2:53-3:2, 12:49-62, 18:6-14.) In the case of PH-ILD, these lung diseases are associated with PH, but many patients also have lung disease without PH. (Anticipated testimony of Dr. Channick.)

25. While there are many causes of interstitial lung disease and many conditions that can be classified as interstitial lung disease, the group is generally heterogenous in nature. (DTX0166, Cottin, Vincent et al., *Fibrosing Interstitial Lung Diseases: Knowns and Unknowns, Eur Respir Rev* 2019:28 180100 (2019) (Introduction) (LIQ\_PH-ILD\_00148627); *see also* Waxman Depo. Tr. at 188:6-16 (“one could say that the disease itself has a heterogeneous nature and in can present in many different ways and patients who have one subset are also heterogeneous as far at the severity, the extent of the disease, so there’s a broad spectrum within each group.”).)

26. A key feature of ILD is the significant lung damage it causes, particularly fibrosis. This damage, along with the reduced oxygen delivery that accompanies it, often results in elevated pressure in the pulmonary circulation, leading to PH. PH-ILD is a chronic and progressive disease, which means that a PH-ILD patient’s condition is expected to worsen over time. (Anticipated testimony of Dr. Channick.) PH-ILD patients are expected to continue worsening even after they receive treatment. (*Id.*; Rajan Saggar Sept. 17, 2024 Depo. Tr. at 162:1-163:2.) PH-ILD will not improve over time and thus there is no “natural course of disease” recovery. Absent therapeutic intervention, a patient with PH-ILD would be expected to have lower 6MWD over time as their exercise capacity continues to decline. Accordingly, improvements in exercise capacity endpoints such as 6MWD in PH-ILD patients after treatment may be viewed as a sign of the treatment’s efficacy.

27. Exacerbations are another characteristic seen in patients with PH-ILD. Exacerbations in patients with PH-ILD refer to significant worsening of respiratory symptoms, often accompanied by new or more widespread abnormalities in lung function. The ’327 patent states that “[a]n exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar

abnormality.” (’327 patent at 22:12-15, 31:4-7.) While the ’327 patent provides a broad definition, it largely aligns with the general understanding of exacerbations as acute episodes marked by increased dyspnea, coughing, and a decline in oxygen saturation, which was well-recognized in the medical community long before the filing date of the ’327 patent. (DTX0048, Gabriela Leuschner & Jürgen Behr, *Acute Exacerbation in Interstitial Lung Disease*, 4 *Frontiers Med.* (2017) (LIQ\_PH-ILD\_00001689) at LIQ\_PH-ILD\_00001690.) In fact, Dr. Aaron Waxman, one of the steering committee members of the INCREASE trial described further below, characterized exacerbations of interstitial lung disease as “worsening oxygenation, worsening shortness of breath which could be due to a flare of their disease, it could be due to infection or it could be due to exposure that just made their disease state worse[,]” which is consistent with the general understanding of exacerbations as recognized in the medical community. (Waxman Depo. Tr. at 115:15-116:2.)

28. Additional exacerbations of respiratory deterioration which can be caused by alveolar abnormalities include increased dyspnea (shortness of breath) and cough as well as decreased oxygen saturation. (DTX0048, Gabriela Leuschner & Jürgen Behr, *Acute Exacerbation in Interstitial Lung Disease*, 4 *Frontiers Med.* (2017) (LIQ\_PH-ILD\_00001689) at LIQ\_PH-ILD\_00001690; *see also* Waxman Depo. Tr. at 115:15-116:2.) These exacerbations were known long before the filing date of the ’327 patent. Improvements in clinical exacerbations correlate with improvements in 6MWD, WHO-FC and FVC. (*See also* Waxman Depo. Tr. at 116:3-18. (testifying that a decrease in shortness of breath (dyspnea) was reflected in the “WHO functional class and [] six-minute walk distance”).)

29. Group 3 PH, which includes PH-ILD, is also categorized as pre-capillary PH. Despite the different WHO categorizations, there is overlap in the hemodynamic profile and

symptoms between Group 1 PAH and Group 3 PH-ILD. (DTX0042, R.C. Deano, et al., *Referral of Patients with Pulmonary Hypertension Diagnoses to Tertiary Pulmonary Hypertension Centers*, *Jama Intern. Med.* 173:10 (2013) (LIQ\_PH-ILD\_00001426) at LIQ\_PH-ILD\_00001427; *see also* Waxman Depo. Tr. at 50:18-51:10); DTX0140, 2017 Waxman Tr. at 3:17-4:10.) Patients often lie on a continuum between Group 1 and Group 3, with patients at one extreme having more severe PH and patients at the other extreme having more severe ILD. (DTX0506, Nathan Barbera 2019 (UTC\_PH-ILD\_219452) at UTC\_PH-ILD\_219455-56 (“[t]he spectrum of severity of both the pulmonary vascular and parenchymal lung disease is likely a continuum[.]”).) Classifying a patient as Group 1 versus Group 3 is often a spectrum and a patient might be classified in a different group depending on the physician. (Anticipated testimony of Dr. Channick; Anticipated testimony of Dr. Nathan.) This overlap is in part due to the fact that the “pathways that are active in patients with PAH are also active in patients with Group 3 and even Group 2 and Group 4 and even Group 5.” (DTX0140, 2017 Waxman Tr. at 3:17-4:4; *see also* Waxman Depo. Tr. at 50:6-51:10 (“In my opinion there were a lot of overlaps between the various groups. When you looked at the pathology, there’s overlap.”); *id.* at 73:1-16 (“[T]here’s overlap in the mechanism driving that disease, and if we have a drug that works in one form, we should be able to re-purpose it to another.”).) There is overlap in what drives the pulmonary vascular remodeling for all groups and many physicians characterize patients who are mixed Group 3 PH-ILD and Group 1 PH patients as having PH-ILD. (Anticipated testimony of Dr. Channick.)

30. While Group 3 PH, including PH-ILD, is classified as pre-capillary PH, its hemodynamic characteristics and symptoms often intersect with those of Group 1 PAH. (DTX0042, Roderick C. Deano, et al., *Referral of Patients with Pulmonary Hypertension Diagnoses to Tertiary Pulmonary Hypertension Centers*, 173 *Jama Intern. Med.* 887 (2013)



(LIQ\_PH-ILD\_00001426) at LIQ\_PH-ILD\_00001427.) In clinical practice, a significant portion of PH patients do not fit neatly into a single classification, reflecting the complex and overlapping nature of these conditions. (Anticipated testimony of Dr. Channick.) For instance, some patients may show signs of severe interstitial lung disease alongside PH typically associated with Group 1. Even in cases where Group 1 features are present, the clinical prominence of ILD leads many physicians to consider these patients as falling primarily within the PH-ILD spectrum—further highlighting the complexity and fluidity of PH classification in real-world medical practice. (*Id.*) To be clear, PH-ILD patients with “severe” or “out-of-proportion” PH, are still PH-ILD patients. (Anticipated testimony of Drs. Channick/Hill.)

31. The diagnosis of PH-ILD can be divided into the diagnosis of the PH component and the diagnosis of the ILD component. To diagnose PH in a patient, physicians may use techniques such as transthoracic echocardiography or right-heart catheterization. (Anticipated testimony of Dr. Channick.) Transthoracic echoes uses ultrasound to image the patient’s heart and estimate the blood pressure in the heart’s pulmonary arteries. (*Id.*) Right heart catheterization is a more invasive procedure that introduces a catheter into the pulmonary artery to observe blood flow through the heart and measure the pressures inside the patient’s heart and lungs. ILD, on the other hand, is a disease that affects the structure of the lungs – structural elements such as elastin and collagen proliferate in the interstitial space between the lung’s alveoli and blood vessels, making the lungs stiffer and more difficult to expand. (*Id.*) The diagnosis of ILD often involves the detection of such changes in the lung’s structure, which can be accomplished using plain x-rays, CT scans, bronchoscopies, and biopsies. (*Id.*) Increased collagen in the lungs can be identified in x-ray and CT scan images. (*Id.*) Bronchoscopies and biopsies involve taking a small

tissue sample of the lungs, which is then analyzed in the lab for its microscopic structure and collagen content. (*Id.*)

32. Physicians can assess effectiveness of PH treatments in PH-ILD patients using hemodynamic parameters, like the mPAP, PVR, and PAWP measures as described in paragraph 15 above. (DTX0040, Channick 2006 at LIQ\_PH-ILD\_00001415.) Changes in hemodynamics are often associated with changes in exercise capacity. For example, a reduction in PVR is generally correlated with improvements in exercise capacity as measured by the 6MWD.

33. Other measures, including brain natriuretic peptide (“BNP”) levels and safety measures such as forced vital capacity (“FVC”), may also be assessed. (*See, e.g.*, DTX0010, R. Saggat, et al., Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis, *Thorax* 69:123-29 (2014) (LIQ\_PH-ILD\_00000226) (“Saggat 2014”) at LIQ\_PH-ILD\_00000227; DTX0363, A. Waxman, et al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, N. Eng. J. Med. 384(4):325 (2021) (UTC\_PH-ILD\_010790) (“NEJM Publication”) at UTC\_PH-ILD\_010809.) FVC measures the volume of air, in mL, that an individual is able to forcibly exhale from their lungs. A higher FVC value indicates better lung function while a lower FVC indicates that a patient has difficulty fully expanding their lungs during inhalation and exhaling effectively. While FVC may be measured in a clinical setting, physicians typically do not examine FVC alone nor do patients directly perceive a change in FVC in their daily lives. As a result, physicians instead focus more generally on how the patient is feeling and functioning, which can be measured by the WHO functional class. The WHO functional class has also been used to demonstrate a reduction in exacerbations associated with an underlying lung disease. (Waxman Depo. Tr. at 116:3-18.)

### III. THE '327 PATENT

34. The '327 patent is entitled "Treatment for Interstitial Lung Disease." (DTX0001, '327 patent at UTC\_PH-ILD\_005310 (Cover).) The '327 patent issued on November 28, 2023. It "claims priority to U.S. provisional application No. 63/011,810 filed Apr. 17, 2020 and U.S. provisional application No. 63/160,611 filed Mar. 12, 2021." (*Id.* at 1:6-10.)

35. The listed inventors on the '327 patent are Leigh Peterson, Peter Smith, and Chunqin ("CQ") Deng. (*Id.* at Cover.)

36. The abstract of the '327 patent states that the patent provides "[m]ethods of treating interstitial lung disease, reducing pulmonary function decline in a subject with [ILD], and increasing [FVC]." (*Id.* at Abstract.)

#### A. Asserted Claims

37. The '327 patent issued with 19 claims, of which only claim 1 is an independent claim. UTC is asserting claims 1-11 and 14-19 of the '327 patent against Liquidia (collectively, the "Asserted Claims"). Claims 1-11 and 14-19 of the '327 patent are reproduced below:

'327 Patent Claims	
Claim 1	
1[a]	A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising
1[b]	administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease
1[c]	an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof
1[d]	in a single administration event that comprises at least 6 micrograms per breath.

'327 Patent Claims	
<b>Claim 2</b>	
2	The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 3</b>	
3	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 4</b>	
4	The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 5</b>	
5	The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 6</b>	
6	The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.
<b>Claim 7</b>	
7	The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.
<b>Claim 8</b>	
8	The method of claim 7, wherein the clinical worsening events comprise at least one hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared to a baseline 6-minute walk distance prior to administering.
<b>Claim 9</b>	

<b>'327 Patent Claims</b>	
9	The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.
<b>Claim 10</b>	
10	The method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 11</b>	
11	The method of claim 1, wherein said administering is performed by a pulsed inhalation device.
<b>Claim 14</b>	
14	The method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.
<b>Claim 15</b>	
15	The method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg.
<b>Claim 16</b>	
16	The method of claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient.
<b>Claim 17</b>	
17	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.
<b>Claim 18</b>	
18	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.
<b>Claim 19</b>	
19	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

38. None of the claims require a Phase 3 clinical trial or a large clinical study, nor do they require the need for FDA approval of inhaled treprostinil in PH-ILD patients. Further, none of the claims recite improvements in 100% of patients administered treprostinil.

39. The claim language of the '327 patent encompasses the entire PH-ILD patient population. It does not exclude any patients. (Anticipated testimony of Drs. Channick/Hill.) The language of claim 1 makes clear that it is directed to “patient[s] having pulmonary hypertension associated with interstitial lung disease,” and nothing in the claim language suggests that PH-ILD patients with so-called “out of proportion PH” or “severe PH” are outside the scope of the claim. The language of the remaining dependent claims likewise does not include any suggestion, or even mention, of out of proportion PH being outside the scope of PH-ILD and Group 3 PH. (*See generally* '327 patent at Claims 2-19.)

40. UTC may try to draw an arbitrary line between “out-of-proportion” or “severe” PH and the PH component of PH-ILD. However, this distinction is not a clinical diagnosis, but rather language used to ensure PH-ILD patients would receive coverage for off-label Tyvaso® prescriptions. (Waxman Depo. Tr. at 214:17-23.) More importantly, the specification of the '327 patent does not distinguish “out-of-proportion” or “severe” PH from normal PH and there is no discussion suggesting that PH-ILD patients with “out-of-proportion” or “severe” PH are excluded from being PH-ILD or Group 3 PH patients. Further, the '327 patent specification's discussion of the INCREASE study, which UTC admits “forms the basis for the specification of the '327 patent,” shows that even the INCREASE study did not exclude patients that Dr. Nathan is expected to object to as having “out-of-proportion” or “severe” PH. (April 23, 2024 Hearing Tr. at 8:7-10.) For example, the '327 patent specification provides that “Group 3 pulmonary hypertension [in the INCREASE study] was defined by pulmonary vascular resistance of *more than* 3 Wood units, ...

and mean pulmonary arterial pressure of 25 mm Hg *or higher.*” (’327 Patent at 28:9-29 (emphasis added).) Additionally, Table 7 of the ’327 patent specification, reproduced below and titled “Additional Baseline Patient Characteristics,” confirms that PH-ILD subject population in the INCREASE study in fact included many patients that UTC now seeks to classify as having “out-of-proportion PH” and having “severe.”

TABLE 7			
Additional Baseline Patient Characteristics.			
	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
6-minute walk distance, meters; mean (range) Median	254.1 (100-538) 256.0	265.1 (30-505) 260.0	259.6 (30-538) 259.0
Pulmonary vascular resistance, Woods units; mean (range) Median	6.369 (3.11-8.05) 5.570	6.013 (3.06-17.62) 5.060	6.191 (3.06-18.05) 5.275
NT-proBNP, pg/mL; mean (range)	1857.53 (10.2-21942.0)	1808.86 (23.0-16297.0)	1832.88 (10.2-21942.0)

TABLE 7-continued			
Additional Baseline Patient Characteristics.			
	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
Median*	550.50	420.80	503.85
Pulmonary arterial pressure, mmHg; mean (range)	37.2 (25-74)	36.0 (25-61)	36.6 (25-74)
Median	35.0	35.0	35.0
Pulmonary capillary wedge pressure, mmHg; mean (range)	10.1 (2-20)	9.6 (0-15)	9.8 (0-20)
Median	10.0	10.0	10.0
Pulmonary function tests			
FEV1% Predicted; mean (range)	63.9 (23, 120)	65.0 (22, 145)	
Median	63.0	63.0	
FVC % Predicted; mean (range)	62.5 (24, 130)	63.8 (20, 134)	
Median	60.0	61.0	
TLC % Predicted; mean (range)	62.9 (25, 126)	64.2 (30, 109)	
Median	62.0	62.5	
DLCO % Predicted; mean (range)	30.0 (5, 86)	28.1 (1, 86)	
Median	29.0	26.0	
DLCO, lung diffusion capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide; TLC, total lung capacity *N = 156 inhaled treprostinil; N = 160 placebo			

(‘327 Patent at UTC\_PH-ILD\_005350-51 (Table 7) (highlighting added).)

Table 7 shows that the patient population in the INCREASE study had an average pulmonary vascular resistance (“PVR”) over 6 Wood units (“WU”) for the treatment group, placebo group, and all patients. (*See id.*) The median PVR also exceeded 5 WU for all groups of patients. (*See id.*) The range of PVR values even show that some patients had PVR values as high as 17.62 WU and 18.05 WU. (*See id.*) The pulmonary arterial pressure (“PAP”) values of Table 7 paint a similar picture—the mean PAP values for all three patient groups exceeded 35 mmHg, the median PAP values were 35.0 mmHg, and the range of PAP values shows that some patients had PAP values of 61 mmHg and 74 mmHg. (*See id.*) In other words, even the ‘327 patent’s description of the



INCREASE study included a majority of patients that UTC may try to classify as “out-of-proportion” or “severe” PH.

**B. The Specification**

41. The '327 patent discloses the method of using treprostinil in the treatment of patients with “pulmonary hypertension due to a condition selected from a chronic lung disease, hypoxia and a combination thereof.” ('327 patent at 1:39-47.) It outlines the therapeutic benefits of treprostinil, a prostacyclin analog, administered via pulsed inhalation devices, which, according to the specification, includes nebulizers and dry powder inhalers. (*Id.* at 13:8-16.)

42. The specification describes WHO Group 3 pulmonary hypertension, and explains that it includes chronic lung disease which can be characterized as obstructive lung disease (commonly COPD), and “emphysema; a restrictive lung disease in which the lungs have a difficult time expanding when one inhales, such as interstitial lung disease or pulmonary fibrosis; sleep apnea; living in an area of high altitude for a long period of time; and various combinations of the above conditions.” (*Id.* at 17:59-18:5.)

43. Claim 1 states that the patient population includes “a patient having pulmonary hypertension associated with interstitial lung disease,” *i.e.*, PH-ILD patients. ('327 patent at Claim 1.)

44. The '327 patent also describes the conditions that are classified as interstitial lung disease, including desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, silicosis, asbestosis, occupational lung

disease, chronic hypersensitivity pneumonitis, idiopathic interstitial pneumonia (IIP), an autoimmune ILD, lymphangioleiomyomatosis (LAM), Langerhans cell histiocytosis (LCH), drug-associated ILD, vasculitis, granulomatosis, berylliosis, and systemic sclerosis-associated interstitial lung disease (SSc-ILD). ('327 patent at 2:53-3:2, 12:49-62, 18:6-14.)

45. Combined pulmonary fibrosis and emphysema (which is often abbreviated in medical literature as “CPFE”), is also a type of ILD. Table 4 of the '327 patent is titled “Characteristics of the Patients at Baseline” and it provides a breakdown of the cause of lung disease in the patients. (*Id.* at UTC\_PH-ILD\_005346-47 (Table 4).) Among the listed causes is “CPFE.” (*Id.*; Anticipated testimony of Dr. Channick.)

46. The specification highlights the ability of treprostinil to improve exercise capacity, reduce pulmonary vascular resistance, and mitigate disease progression in patients with PH-ILD. According to the specification, these methods address the challenges associated with traditional therapies, emphasizing localized delivery to the lungs to optimize efficacy while minimizing systemic side effects.

47. The specification further provides a discussion of dosing regimens, pharmacokinetics, and the potential use of treprostinil in combination with other therapeutic agents. It also describes the challenges of achieving effective treatment outcomes in PH-ILD patients and the significance of utilizing inhaled formulations for target therapies. The specification also includes a list of dosing regimens, including, for example, the number of breaths to take “in a single administering event,” ('327 patent at 21:20-35) the number of “single administering events per day,” (*id.* at 21:43-48) and the dosage of each single administering event(*id.* at 21:36-42).

48. The '327 patent also describes a variety of ways in which a patient may benefit from the use of treprostinil, including an increase in 6MWD (*id.* at 18:15-45), reduction in plasma concentration of NT-proBNP (*id.* at 18:46-19:5), reduction in the number of exacerbations of the chronic lung disease (*id.* at 19:6-32), a reduction in the number of clinical worsening events, (*id.* at 19:33-60) and an improvement in forced vital capacity, (percent predicted) (*id.* at 19:61-20:43).

49. To illustrate these principles, the specification discloses five examples, as described below.

50. Example 1 describes a clinical study evaluating the effects of inhaled treprostinil on patients with underlying lung disease, focusing on exacerbations and pulmonary function improvements. (*Id.* at 22:9-25:43.) The study defines exacerbations of underlying lung disease as acute, clinically significant, respiratory deteriorations characterized by evidence of new widespread alveolar abnormality. (*Id.* at 22:12-15.)

51. Patients were administered inhaled treprostinil or placebo over a 16-week period, beginning at a dose of 3 breaths (6 mcg each, 18 mcg total) four times daily, with escalation allowed every three days to a target dose of 9 breaths (54 mcg) four times daily and a maximum of 12 breaths (72 mcg), as clinically tolerated. (*Id.* at 22:19-36.) The study mentions several endpoints, including 6-minute walk distance ("6MWD"), plasma NT-proBNP concentrations, time to clinical worsening, and pulmonary function tests. Notably, however, Example 1 does not report results for 6MWD, plasma NT-proBNP, time to clinical worsening, or improvements in exercise capacity. (*Id.* at 22:9-25:43.) These endpoints are listed as part of the study design, but no data is provided in the example to support claims related to these measures. (*Id.*) Moreover, there is no data provided in Example 1 that corresponds to an improvement in exercise capacity. (*Id.*)

52. The results reported focus on the reduction in exacerbations of underlying lung disease. The specification states that “exacerbation(s) may include an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread abnormality.” (’327 patent at 19:30-32, 22:12-15.) The inhaled treprostinil group experienced a 26.4% exacerbation rate compared to 38.7% in the placebo group, representing a statistically significant 34% reduction in exacerbation risk. (*Id.* at 22:45-50.)

53. Example 1 also provides results of forced vital capacity (FVC). FVC values can be provided as an absolute FVC, denoted in mL, or a percent predicted FVC value, denoted as % predicted. FVC is a measure of the volume of air an individual may exhale from their lungs, and not a measure of exercise capacity.

54. Example 1 does not disclose a statistically significant p-value for improvements of FVC within the treatment group compared to baseline, but instead discloses it for the difference between FVC in the treated versus placebo patient population. (’327 patent at UTC\_PH-ILD\_005344-45 (Tables 1-3).) It also discloses the % FVC change from baseline with subsets of the PH-ILD population including ITT, IIP, and IPF groups.

55. For the “Overall” Intent to Treat (“ITT”) population of Example 1, there was no statistically significant improvement in absolute FVC, but a statistically significant improvement in % predicted FVC. (*Id.* at UTC\_PH-ILD\_005344 (Table 1).) It also shows a 0.77% change in FVC over baseline at week 8. (*Id.*)

56. Table 2 shows an analysis of FVC data for the idiopathic interstitial pneumonia intent-to-treat (IIP-ITT) population. (*Id.* at UTC\_PH-ILD\_005344 (Table 2).) Only the “between group differences for % predicted FVC were statistically significant at Week 8.” (*Id.* at 25:32-34.)

It also shows a 0.92% and 1.66% change in FVC over baseline at week 8 and week 16, respectively, for the IIP population.

57. Table 3 also shows a further subgroup analysis of Example 1 in patients with idiopathic pulmonary fibrosis (“IPF”), which is a subgroup of the IIP patients from Table 2. For this subgroup, inhaled treprostinil improved FVC by 84.52 mL at week 8, which was not statistically significant, and 168.52 mL at week 16, which was statistically significant. (*Id.* at UTC\_PH-ILD\_005345 (Table 3).) This data shows a 1.60% and 1.62% change in FVC over baseline at week 8 and week 16, respectively, for the IPF population.

Table 3: Analysis of FVC Data Using Mixed Model Repeated Measurement for Subjects with IPF - ITT for IIP Subjects							
		IPF		FVC (mL)			
Week 8	Inhaled treprostinil	31	41.69	Inhaled treprostinil - Placebo	84.522	-20.409, 189.454	0.1128
	Placebo	47	-42.83				
Week 16	Inhaled treprostinil	28	38.24	Inhaled treprostinil - Placebo	168.524	40.078, 296.970	0.0108
	Placebo	42	-130.3				
				FVC (% predicted)			
Week 8	Inhaled treprostinil	31	1.60	Inhaled treprostinil - Placebo	2.543	0.145, 4.941	0.0380
	Placebo	47	-0.94				
Week 16	Inhaled treprostinil	28	1.62	Inhaled treprostinil - Placebo	3.504	0.712, 6.295	0.0147
	Placebo	42	-1.88				

Abbreviations:  
 CI, confidence interval;  
 FVC, forced vital capacity;  
 IPF, idiopathic pulmonary fibrosis;  
 ITT, Intent-to-Treat;  
 LS, least square; MMRM, mixed model repeated measurement  
 LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

58. The next example, Example 2, is not written in past tense and provides no indication it was actually performed. (*Id.* at 25:44-62.) These types of patent examples are called “prophetic examples.” (Anticipated testimony of Dr. Channick.) Example 2 claims to be designed to evaluate the efficacy of treprostinil for treating chronic fibrosing interstitial lung diseases (“CF-ILDs”),

including idiopathic interstitial pneumonias (“IIPs”), IPF, chronic hypersensitivity pneumonitis (“CHP”), and environmental/occupational fibrosing lung disease. (’327 patent at 25:44-62.) The example proposes a study where patients are treated with inhaled treprostinil at a dosage of up to 15 breaths, administered four times daily (“QID”), based on tolerability. (*Id.*) The primary efficacy endpoint is defined as the change from baseline to week 24 in FVC, measured as either an absolute or percent-predicted change. (*Id.*)

59. Example 3, entitled “Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease” describes a completed clinical study evaluating the effects of inhaled treprostinil on patients with PH-ILD called INCREASE. (Anticipated testimony of Dr. Channick; Smith Depo. Tr. at 62:4-65:1; Peterson Depo. Tr. at 120:12-122:7.)

60. The study is a randomized, double-blind, placebo-controlled trial involving PH-ILD patients treated with either inhaled treprostinil or placebo. (’327 patent at 26:36-50.) Patients began with a dose of 3 breaths (18 mcg) four times daily, with a protocol allowing dose escalation every three days as tolerated, up to a target dose of 9 breaths (54 mcg) and a maximum dose of 12 breaths (72 mcg). (*Id.*)

61. The results demonstrate statistically significant improvements in exercise capacity as measured by the 6MWD. (*Id.* at 26:52-27:3.) The analysis also reveals a reduction in the occurrence of clinical worsening in the treatment group compared to the placebo group. (*Id.*) In addition, the study reports improvements in secondary endpoints, including a reduction in plasma NT-proBNP levels and stabilization or improvement of pulmonary function metrics, such as FVC. (*Id.*, *id.* at UTC\_PH-ILD\_005353 (Table 10).)

62. Example 4 describes a randomized study of 36 healthy individuals to compare the pharmacokinetics of the nebulized inhaled treprostinil (“Tyvaso nebulizer”) and treprostinil

inhalation powder (“TreT”). (’327 patent at UTC\_PH-ILD\_005355-5356.) Example 5 focuses on the safety and tolerability of TreT delivered via a dry powder inhaler in subjects with pulmonary arterial hypertension (“PAH”) who were being treated with Tyvaso. (*Id.* at UTC\_PH-ILD\_005356-358.)

**C. Prosecution History**

63. U.S. Patent Application No. 17/233,061 (“061 application”), which led to the ’327 patent, was filed on April 16, 2021, and claims priority to two provisional applications: U.S. Provisional Application No. 63/011,810 (“’810 provisional”) filed April 17, 2020 and U.S. Provisional Application No. 61/160,611 (“’611 provisional”), filed March 12, 2021.

**a. Priority App. 1: U.S. Provisional App. No. 63/011,810, filed Apr. 17, 2020**

64. The ’810 provisional application was filed on April 17, 2020.

65. Like the ’327 patent, the title of the ’810 provisional is, “TREATMENT FOR INTERSTITIAL LUNG DISEASE.” (DTX0375, (“’810 provisional”) at UTC\_PH-ILD\_069472.) Similarly, the named inventors listed on the ’810 provisional are Leigh Peterson, Peter Smith, and Chunqin Deng. (*Id.*) The ’810 provisional was assigned to United Therapeutics Corporation and was filed by the applicant’s representative, registered patent attorney Stephen B. Maebius. (*Id.* at UTC\_PH-ILD\_069473; Maebius Depo. Tr. at 28:10-12.)

66. The Background section of the ’810 provisional identifies interstitial lung disease (“ILD”) as a group of diseases affecting the interstitium of the lungs, including tissue around alveoli and other pulmonary structures. (’810 provisional at [0002].) The ’810 provisional includes examples 1 and 2 from the issued ’327 patent, which were described above in Section III.B, but does not include any of the other examples that are present in the issued ’327 patent. (*Id.* at [0080]-[0090].)

67. Although the '810 provisional claims a method of treating interstitial lung disease (ILD) generally, it does not claim a method of treating PH-ILD, specifically. (*See generally* '810 provisional.) [REDACTED] (*See e.g.*, Smith Depo. Tr. at 71:10-72:18.)

68. [REDACTED]  
[REDACTED]  
[REDACTED]

(*See e.g.*, Smith Depo. Tr. at 57:10-59:8, 65:9-71:9; *see infra* Section X.)

**b. Priority App. 2: U.S. Provisional App. No. 63/160,611, filed Mar. 12, 2021**

69. The '611 provisional was filed on March 12, 2021 by the applicants' representative, registered patent attorney Stephen B. Maebius. (DTX0376, ("611 provisional application specification") at UTC\_PH-ILD\_069551.)

70. Like the '327 patent, the '611 provisional is titled, "TREATMENT FOR INTERSTITIAL LUNG DISEASE." (DTX0376, '611 provisional application specification at UTC\_PH-ILD\_069551.) Similarly, the named inventors listed on the '611 provisional are Leigh Peterson, Peter Smith, and Chunqin Deng. (*Id.* at UTC\_PH-ILD\_069628.)

71. The Background of the '611 provisional similarly identifies ILD as a group of diseases affecting the interstitium of the lungs. (*Id.* at UTC\_PH-ILD\_069551.)

72. The '611 provisional includes the same Examples 1 and 2 as the '810 provisional, but the '611 provisional includes additional examples, Example 3–5, which were described above in paragraphs 59-62.

**c. April 16, 2021: As-Filed Application (U.S. App. No. 17/233,061) Leading to the '327 Patent**

73. The application that issued as the '327 patent was filed on April 16, 2021 and was assigned application No. 17/233,061 (the "'061 application"). ('327 patent at UTC\_PH-



ILD\_005310.) Leigh Peterson, Peter Smith, and Chunqin Deng were named as the inventors. (*Id.*) The '061 application was assigned to United Therapeutics Corporation and was filed by the applicant's representative, registered patent attorney Stephen B. Maebius. (*Id.*; Maebius Depo. Tr. at 160:15-161:18, 170:7-16.)

74. The specification included the following information regarding any priority claim to related applications:

<p style="text-align: center;"><b>RELATED APPLICATIONS</b></p> <p>The present application claims priority to U.S. provisional application No. 63/011,810 filed April 17, 2020 and U.S. provisional application No. 63/160,611 filed March 12, 2021, each of which is incorporated herein by reference in its entirety.</p>
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(DTX0334, ("327 patent file history") UTC\_PH-ILD\_009419 at UTC\_PH-ILD\_009423.)

75. The as-filed specification is the same as the specification issued in the '327 patent.

76. The claims that were originally filed with the '061 application are reproduced below:

Claim No.	Limitation
1	A method of treating a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprising administering to a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of treprostinil, a prodrug thereof or a pharmaceutically acceptable salt thereof.
2	The method of claim 1, wherein the pulmonary hypertension in the subject is a pulmonary hypertension due to a chronic lung disease
3	The method of claim 1, wherein the chronic lung disease comprises chronic obstructive pulmonary disease, emphysema, interstitial lung disease, pulmonary fibrosis and a combination thereof.
4	The method of claim 1, wherein the pulmonary hypertension is pulmonary hypertension associated with interstitial lung disease.

5	The method of claim 1, wherein the chronic lung disease comprises idiopathic interstitial pneumonia, chronic hypersensitivity pneumonitis, occupational lung disease, pulmonary fibrosis, emphysema, connective tissue disease or a combination thereof
6	The method of claim 5, wherein the chronic lung disease comprises idiopathic interstitial pneumonia.
7	The method of claim 6, wherein the idiopathic interstitial pneumonia is selected from idiopathic pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia, respiratory bronchiolitis, desquamative interstitial pneumonia.
8	The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the subject after 8 weeks, 12 weeks or 16 weeks of the administering.
9	The method of claim 1, wherein said administering increases a 6 minutes walk distance by at least 10 m after 8 weeks, 12 weeks or 16 weeks of the administering.
10	The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the subject after 8 weeks, 12 weeks or 16 weeks of the administering.
11	The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the subject by at least 200 pg/ml after 8 weeks, 12 weeks or 16 weeks of the administering.
12	The method of claim 1, wherein said administering provides a statistically significant reduction of a number of exacerbations of the chronic lung disease
13	The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the chronic lung disease.
14	The method of claim 13, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.
15	The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the subject after 8 weeks, 12 weeks or 16 weeks of the administering.

16	The method of claim 15, wherein said administering improves the forced vital capacity (FVC) in the subject by at least 20 ml after 8 weeks, 12 weeks or 16 weeks of the administering.
17	The method of claim 1, wherein said administering is performed by inhalation.
18	The method of claim 17, wherein said administering is performed by a pulsed inhalation device.
19	The method of claim 18, wherein the pulsed inhalation device contains an inhalation solution comprising treprostinil or a pharmaceutically acceptable salt thereof.
20	The method of claim 18, wherein the pulsed inhalation device is a nebulizer.
21	The method of claim 18, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.
22	The method of claim 17, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the subject in a single inhalation administration event is from 15 µg to 100 µg.
23	The method of claim 22, wherein the single inhalation administration event does not exceed 15 breaths by the subject

(DTX0334, '327 patent file history at UTC\_PH-ILD\_009496-498.)

77. Claim 1 is the only independent claim and claims 2-23 are dependent claims.

**d. May 12, 2021: IDS No. 1**

78. On May 12, 2021, UTC, through its counsel, filed its first information disclosure statement ("IDS"), disclosing 136 references to be considered by the examiner. (*See id.* at UTC\_PH-ILD\_009537.)

**e. Sept. 21, 2021: IDS No. 2**

79. On September 21, 2021, UTC, through its counsel, filed its second IDS, disclosing seven references to be considered by the examiner. (*Id.* at UTC\_PH-ILD\_009555.)

**f. Feb. 16, 2022: IDS No. 3 and Preliminary Amendment**

80. On February 16, 2022, before hearing back from the examiner regarding the application, UTC, through its counsel, filed a preliminary amendment canceling claim 17, amending claims 1, 18, 22, and 23, and adding new claims 24-26, as reproduced below:

Claim No.	Limitation
1	(Currently Amended) A method of treating a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprising administering <u>by inhalation</u> to a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of treprostinil, <del>a prodrug thereof</del> or a pharmaceutically acceptable salt thereof <u>in an amount of at least 6 micrograms per breath.</u>
17	(Canceled)
18	(Currently Amended) The method of claim 1 <u>[[17]]</u> , wherein said administering is performed by a pulsed inhalation device.
22	(Currently Amended) The method of claim 1 <u>[[17]]</u> , wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the subject in a single inhalation administration event is from 15 µg to 100 µg.
23	(Currently Amended) The method of claim 22, wherein the single inhalation administration event does not exceed 15 breaths by the subject.
24	(New) The method of claim 1, wherein said administering increase a 6 minutes walk distance in the subject by at least 10 m after 8 weeks of the administering.
25	(New) The method of claim 1, wherein said administering increase a 6 minutes walk distance in the subject by at least 15 m after 12 weeks of the administering.
26	(New) The method of claim 1, wherein said administering increase a 6 minutes walk distance in the subject by at least 15 m after 16 weeks of the administering.

(*Id.* at UTC\_PH-ILD\_009605-608.)

81. In addition to amending the claims, UTC, through its counsel, filed its third IDS, disclosing 329 references to be considered by the examiner. (*Id.* at UTC\_PH-ILD\_009616-632.)

Of the 329 references, UTC, through its counsel, disclosed various references that are relevant to issues in this litigation, including the references highlighted below:

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>ii</sup>
	C120	De Wet et al., "Inhaled prostacyclin is safe, effective and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery," J. Thoracic Cardiovasc. Surg., 2004, 127:1058-1067.	
	C121	Defendant Watson Laboratories, Inc.'s Invalidity Contentions for U.S. Patent Nos. 9,339,507 and 9,358,240, in The United States District Court for the District of New Jersey, Civil Action No. 3:15-cv-05723-PGS-LHG, August 5, 2016, 56 pages.	

(Id. at UTC\_PH-ILD\_009620.)

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>ii</sup>
	C273	ORENITRAM label, October 2019, 17 pages.	
	C274	Osterweil, Neil, "Treprostinil Improves Walk Distance in Pulmonary Hypertension," July 9, 2020, 9 pages, <a href="http://www.medscape.com/viewarticle/933674">www.medscape.com/viewarticle/933674</a> ,	
	C275	Pappert et al., "Aerosolized Prostacyclin Versus Inhaled Nitric Oxide in Children with Severe Acute Respiratory Distress Syndrome," Anesthesiology, June 1995, 82(6):1507-1511.	
	C276	Petition for Inter Partes Review of U.S. Patent No. 10,716,793, Liquidia Technologies, Inc. (petitioner) v. United Therapeutics Corporation (patent owner), IPR2021-00406, and Exhibits 1002, 1003, 1004, 1005 and 1036.	

(Id. at UTC\_PH-ILD\_009629.)

	C315	Watson Laboratories, Inc. (Petitioner) v. United Therapeutics Corp. (Patent Owner), Decision Granting Institute of Inter Partes Review 37 C.F.R. 42.108, IRP2017-01621, Patent No. 9,358,240, January 11, 2018.	
	C316	Watson Laboratories, Inc. (Petitioner) v. United Therapeutics Corp. (Patent Owner), Decision Granting Institute of Inter Partes Review 37 C.F.R. 42.108, IRP2017-01622, Patent No. 9,339,507, January 11, 2018.	
	C317	Watson Laboratories, Inc. (Petitioner) v. United Therapeutics, Inc. (Patent Owner), Petition for Inter Partes Review, IRP2017-01621, Patent No. 9,358,240, with only Exhibits 1002, 1059, 1161 and 1164 and not including exhibits already provide with C318.	
	C318	Watson Laboratories, Inc. (Petitioner) v. United Therapeutics, Inc. (Patent Owner), Petition for Inter Partes Review, IRP2017-01622, Patent No. 9,339,507, with all Exhibits on exhibit list.	
	C319	Waxman et al., "Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease," The New England Journal of Medicine, 2021, 284:325-334.	

(Id. at UTC\_PH-ILD\_009631.)

82. Across the three IDS submissions, UTC submitted a total of 472 references to the Examiner, and yet, as discussed below in Section XII, still failed to submit several material references to the USPTO.



**g. Mar. 6, 2023: Office Action**

83. On March 6, 2023, the Examiner rejected all the claims as anticipated based on *Malinin et al.* (WO2015/138423) (“*Malinin*”), *Zhang et al.* (WO2016/205202) (“*Zhang*”), *Morgans et al.* (WO2012/009097) (“*Morgans*”), *Wade et al.* (WO2008/098196) (“*Wade*”), and *Bosc et al.* (WO2016/176399) (“*Bosc*”). (DTX0334, '327 patent file history at UTC\_PH-ILD\_009706-709.)

84. The Examiner stated that under 35 U.S.C. 102(a)(1), all the claims are anticipated by *Malinin*, which discloses methods of treating PH due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil:

1. Claims 1-16 and 18-26 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by *Malinin et al.* (WO2015/138423).

Applicant claims methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil.

This reference discloses methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil. (See Abstract and pages 3-10, 74-78, and Tables). These methods read on the instant claim. Since this reference teaches the exact methods, Applicant's claims are anticipated, and thus, rejected under 35 U.S.C. 102.

(*Id.* at UTC\_PH-ILD\_009707.)

85. Similarly, the Examiner stated that under 35 U.S.C. § 102(a)(1), all the claims are anticipated by *Zhang*, *Morgans*, *Wade*, and *Bosc*, each of which disclose methods of treating PH due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil:

2. Claims 1-16 and 18-26 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Zhang et al. (WO2016/205202).

Applicant claims methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil.

This reference discloses methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil. (See Abstract and pages 1-3, 35-39 and 83). These methods read on the instant claim. Since this reference teaches the exact methods, Applicant's claims are anticipated, and thus, rejected under 35 U.S.C. 102.

(DTX0334, '327 patent file history at UTC\_PH-ILD\_009707-708.)

3. Claims 1-16 and 18-26 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Morgans et al. (WO2012/009097).

Applicant claims methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil.

This reference discloses methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil. (See Abstract and pages 1-3, 53-60, Figures and Examples). These methods read on the instant claim. Since this reference teaches the exact methods, Applicant's claims are anticipated, and thus, rejected under 35 U.S.C. 102.

(Id. at UTC\_PH-ILD\_009708.)

4. Claims 1-16 and 18-26 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Wade et al. (WO2008/098196).

Applicant claims methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil.

This reference discloses methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil. (See Abstract and pages 3-10, 21-22 and Examples). These methods read on the instant claim. Since this reference teaches the exact methods, Applicant's claims are anticipated, and thus, rejected under 35 U.S.C. 102.

(*Id.* at UTC\_PH-ILD\_009708-709.)

5. Claims 1-16 and 18-26 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Bosc et al. (WO2016/176399).

Applicant claims methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil.

This reference discloses methods for treating pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof with treprostinil. (See Abstract and pages 2-12 and 43-50, and Examples).

These methods read on the instant claim. Since this reference teaches the exact methods, Applicant's claims are anticipated, and thus, rejected under 35 U.S.C. 102.

(*Id.* at UTC\_PH-ILD\_009709.)

#### **h. May 10, 2023: UTC's Amendment and Response**

86. UTC, through its counsel, responded to the Examiner's March 6, 2023 rejections on May 10, 2023. (*Id.* at UTC\_PH-ILD\_009738.) To overcome the rejections, UTC, through its counsel, canceled claims 2-7, and amended claims 1, 8-13, 15-16, and 22-26, as reproduced below:



Claim No.	Limitation
1	(Currently Amended) A method of <u>improving exercise capacity in a patient having <del>treating</del> a pulmonary hypertension associated with interstitial lung disease due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises <del>an amount of</del> at least 6 micrograms per breath.</u>
2-7	(Canceled)
8	(Currently Amended) The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the <u>patient</u> <del>subject</del> after 8 weeks, 12 weeks <sub>2</sub> or 16 weeks of the administering.
9	(Currently Amended) The method of claim 1, wherein said administering increases a 6 minutes walk distance <u>of the patient</u> by at least 10 m after 8 weeks, 12 <sub>2</sub> weeks or 16 weeks of the administering.
10	(Currently Amended) The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the <u>patient</u> <del>subject</del> after 8 weeks, 12 <sub>2</sub> weeks or 16 weeks of the administering.
11	(Currently Amended) The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the <u>patient</u> <del>subject</del> by at least 200 pg/ml after 8 weeks, 12 weeks <sub>2</sub> or 16 weeks of the administering.
12	(Currently Amended) The method of claim 1, wherein said administering provides a statistically significant reduction of <del>a number of</del> at least one exacerbations of the <u>interstitial lung disease</u> <del>chronic lung disease</del> .
13	(Currently Amended) The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the <u>interstitial lung disease</u> <del>chronic lung disease</del> .
14	The method of claim 13, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.

15	(Currently Amended) The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the <u>patient subject</u> after 8 weeks, 12 <sub>2</sub> weeks or 16 weeks of the administering.
16	(Currently Amended) The method of claim 15, wherein said administering improves the forced vital capacity (FVC) in the <u>patient subject</u> by at least 20 ml after 8 weeks, 12 weeks <sub>2</sub> or 16 weeks of the administering.
17	(Canceled)
18	(Previously presented) The method of claim 17, wherein said administering is performed by a pulsed inhalation device.
22	(Currently Amended) The method of claim 17, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the <u>patient subject</u> in a single inhalation administration event is from 15 µg to 100 µg.
23	(Currently Amended) The method of claim 22, wherein the single inhalation administration event does not exceed 15 breaths by the <u>patient subject</u> .
24	(Currently Amended) The method of claim 1, wherein said administering <del>increase</del> <u>increases</u> a 6 minutes walk distance <u>of</u> <del>[[in]]</del> the <u>patient subject</u> by at least 10 m after 8 weeks of the administering.
25	(Currently Amended) The method of claim 1, wherein said administering <del>increase</del> <u>increases</u> a 6 minutes walk distance <u>of</u> <del>[[in]]</del> the <u>patient subject</u> by at least 15 m after 12 weeks of the administering.
26	(Currently Amended) The method of claim 1, wherein said administering <del>increase</del> <u>increases</u> a 6 minutes walk distance <u>of</u> <del>[[in]]</del> the <u>patient subject</u> by at least 15 m after 16 weeks of the administering.

(*Id.* at UTC\_PH-ILD\_009738-741.)

87. Notably, independent claim 1 was amended by narrowing:

- a. the method (“treating” to “improving exercise capacity”),
- b. the disease (“pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof” to “PH-ILD”), and

- c. the dose (“an effective amount” to “an effective amount of at least 15 micrograms up to a maximum tolerated dose” and “an amount of” to “a single administration event that comprises”).
88. The changes to independent claim 1 are highlighted in the following table:

Claim 1: 02/16/2022 Amendment	Claim 1: 03/10/2023 Amendment
A method of treating	A method of improving exercise capacity
	in a patient having
a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof,	pulmonary hypertension associated with interstitial lung disease
comprising administering by inhalation to a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof	comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease
an effective amount of treprostinil, or a pharmaceutically acceptable salt thereof	an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof
in an amount of at least 6 micrograms per breath.	in a single administration event that comprises at least 6 micrograms per breath.

89. Along with amending the claims, UTC, through its counsel, addressed how each of the cited references did not disclose each and every requirement of the amended claims:

- a. *Malinin*: UTC argued, “Malinin teaches nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breath. Thus, Malinin is not an anticipatory reference because Malinin does not teach all the elements of amended claim 1.”
- b. *Wang*: UTC argued, “Wang teaches nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breath. Furthermore, Wang

teaches nothing regarding improving exercise capacity in any patient. In sum, Wang is not an anticipatory reference because Wang does not teach all the elements of amended claim 1.”

- c. *Morgans*: UTC argued, “Morgans teaches nothing regarding administering treprostinil by inhalation. Applicant's computerized search revealed that Morgans mentions a word starting with ‘inhal’ only once in paragraph [0147], when Morgans states that ‘the mitotic kinesin inhibitor is administered intrapulmonarily by inhalation.’ However, treprostinil is not the mitotic kinesin inhibitor administered in Morgans by inhalation, so this statement is not relevant to the instant claims. Because Morgans teaches nothing regarding administering treprostinil by inhalation, Morgans teaches nothing about treprostinil doses for inhalation or an amount of treprostinil administered per breath. Furthermore, Morgans teaches nothing regarding improving exercise capacity in any patient.”
- d. *Wade*: UTC argued, “Wade does not teach or suggest ‘a single administration event that comprises at least 6 micrograms per breath’ as amended claim 1 recites.”
- e. *Bosc*: UTC argued, “Bosc teaches nothing regarding administering treprostinil by inhalation. Bosc mentions treprostinil in paragraph [0009] as a second therapeutic to be used together with Bosc's retinoic acid receptor-related orphan nuclear receptor (ROR) inhibitor. However, Bosc does not teach or suggest that the second therapeutic, such as treprostinil, is administered by inhalation. Because Bosc teaches nothing regarding administering treprostinil by inhalation, Bosc also teaches nothing about either treprostinil doses for inhalation or an amount of

treprostinil administered per breath. Furthermore, Bosc teaches nothing regarding improving exercise capacity in any patient.”

(DTX0334, '327 patent file history at UTC\_PH-ILD\_009742-745.)

**i. June 28, 2023: Notice of Allowance**

90. In response to UTC's May 10, 2023 amendments and remarks, the Examiner allowed the asserted claims of the '327 patent, and provided the following reasons for allowance:

**REASONS FOR ALLOWANCE**

The following is an examiner's statement of reasons for allowance: the methods were not found to be obvious or anticipated by the prior art of record. The prior art does not teach or suggest the methods encompassing compounds substituted in the manner claimed by the Applicant.

(*Id.* at UTC\_PH-ILD\_009754.)

**D. Person of Ordinary Skill in the Art**

91. A POSA would have a medical degree with a specialty in pulmonology or cardiology, plus at least two years of experience treating patients with PH as an attending, including PH associated with ILD and including with inhaled therapies, or equivalent degree or experience. (Anticipated testimony of Dr. Channick.)

92. Liquidia's experts, Dr. Channick and Dr. Hill, possess at least ordinary skill in the art and are able to provide opinions reflecting the perspective of a POSA.

93. Liquidia's expert, Dr. Ogenstad, offers his opinion to the extent it is determined that a non-POSA biostatistician's perspective is relevant to the issues in this case. To the extent UTC asserts Dr. Thisted's opinions reflects the perspective of a POSA, so do Dr. Ogenstad's opinions.

#### IV. CLAIM CONSTRUCTION

94. The parties submitted a joint brief on claim construction on August 29, 2024 asking the Court to construe the terms “a”/“the” in multiple claims, “maximum tolerated dose,” and “pulsed inhalation device.” (D.I. 123.) The parties agreed that the preamble of claim 1—“[a] method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease”—is limiting. (*Id.* at 5.) The hearing on claim construction occurred on September 30, 2024. On October 21, 2024, the Court construed the disputed terms within the Asserted Claims as follows:

Term	Construction
“a”/“the” in the following terms:  “a patient,” “the patient,” “a maximum tolerated dose,” “a single administration event,” “the administering,” and “the single inhalation administration event”  ’327 patent, claims 1-5, 8-10, and 15-19	“one or more”
“maximum tolerated dose”  ’327 patent, claim 1	plain and ordinary meaning; not indefinite
“pulsed inhalation device”  ’327 patent, claims 11 and 14	“a device that provides for non-continuous inhaled drug delivery”

(D.I. 155.)

95. Each of the dependent Asserted Claims require either a “statistically significant” result (claims 2, 4, 6, 7-8, 9-10) or a particular clinical outcome that must be measured (claims 3, 5, 17-19). To determine if the result of a particular intervention is statistically significant, a person must select a parameter to measure, apply the intervention to a sufficiently large group to detect a meaningful difference, measure the selected parameter in each group member, aggregate the collected data, and perform statistical analysis on the data. (Anticipated testimony of Dr. Channick/Ogenstad; D.I. 123 at 11.) For claims that do not require a statistically significant result,

the claims at least require a measurement of the claimed result. (*Id.*) For example, claim 17 requires a physician or patient to perform the “method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.” (’327 patent at Claim 17.)

96. UTC asserts that for infringement the dependent claims of the ’327 patent do not require any additional steps, including any measurement or analysis steps, beyond those necessary to perform claim 1. (Anticipated testimony of Drs. Nathan/Thisted.) Even for claim 1, UTC maintains that a physician only needs to write a prescription for inhaled treprostinil to treat PH-ILD patients to satisfy the limitations of claim 1. (*Id.*) Drs. Nathan and Thisted further explained that the dependent claims are merely directed to the intended results of claim 1 and that the claim language in the dependent claims describes results that would be seen in the population. Thus, UTC’s experts opine that these limitations are intrinsically met by the INCREASE study and no additional steps or outcomes beyond prescribing inhaled treprostinil is needed. (*Id.*)

97. To the extent the Court adopts UTC’s interpretation, then the dependent claims are directed to an intended result and have no patentable weight and thus the recited elements have no bearing on validity. (Anticipated testimony of Dr. Channick.)

## **V. SCOPE OF THE PRIOR ART**

### **A. Inhaled Treprostinil Becomes FDA Approved for Treating PAH: Tyvaso®**

#### **1. Early Use of Treprostinil**

98. Treprostinil is a drug belonging to a class of compounds known as prostacyclin analogs that are used to treat PH. Prostacyclin analogs act as pulmonary vasodilators, meaning they relax the muscle in the pulmonary arteries and thereby decrease the resistance to the flow of blood.

99. Treprostinil is not a new drug. As the '327 patent recognizes, treprostinil is the active ingredient in several approved therapies for pulmonary arterial hypertension. ('327 patent at 8:1-18.) In 2002 and 2004, treprostinil was approved under the brand name Remodulin® for subcutaneous and intravenous administration in patients with pulmonary arterial hypertension (PAH) (WHO Group 1) “to diminish symptoms associated with exercise.” (DTX0052, Remodulin Label, NDA 21-272/S-005 (LIQ\_PH-ILD\_00002444) at LIQ\_PH-ILD\_00002447; '327 patent at 8:1.)

100. In 2009, the FDA approved an inhaled version of treprostinil called Tyvaso® for treating “pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance.” (DTX0357, 2009 Tyvaso® Label (UTC\_PH-ILD\_010692) at UTC\_PH-ILD\_010693.) Tyvaso® was also approved in 2021 for PH-ILD “to improve exercise ability.” (DTX0360, 2021 Tyvaso® Label (UTC\_PH-ILD\_010744) at UTC\_PH-ILD\_010744.) Tyvaso® is a liquid formulation of treprostinil, which is delivered to a patient as a mist via a pulsed nebulizer. (*Id.* at UTC\_PH-ILD\_010693–94.) Tyvaso® has since been approved, in 2022, in a different formulation for administration using a dry-powder inhaler called Tyvaso DPI®.

101. By 2006 and at least by 2009, inhaled treprostinil was known to improve exercise capacity in patients with pre-capillary. (DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010693; DTX0040, R.N. Channick, et al., Safety and Efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension, *J. Am. Coll. Cardiol.* 48(7):1433 (2006) (LIQ\_PH-ILD\_00001414) (“Channick 2006”); *see generally* DTX0002, '793 patent.) Then, as now, physicians commonly measured exercise capacity in the Six-Minute Walk Test (“6MWT”), which, as noted above, measures how far a patient can walk (the 6-minute walk distance or “6MWD”) in six minutes. The 6MWT can also be used to demonstrate a reduction in clinical



worsening (*see* claim 8 of the '327 patent) and a reduction in clinical exacerbations of lung disease, including interstitial lung disease (Waxman Depo. Tr. at 116:3-18. (testifying that a decrease in shortness of breath (dyspnea) was reflected in the “WHO functional class and [] six-minute walk distance”)).

## **2. 2009 Tyvaso Label**

102. As mentioned above, in 2009, the FDA approved an inhaled version of treprostinil called Tyvaso® for treating “pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance.” (DTX0357, 2009 Tyvaso® Label (UTC\_PH-ILD\_010692) at UTC\_PH-ILD\_010693.)

103. Section 1 of the 2009 Tyvaso® Label states that the dosing regimen described in Section 2 will result in “increase[d] walk distance in patients with WHO Group I pulmonary arterial hypertension and NYHA Class III symptoms.” (*Id.* at UTC\_PH-ILD\_010694.)

104. Section 2 of the 2009 Tyvaso® Label describes the dosing and administration of inhaled treprostinil to PAH patients. (*Id.*) The initial dose “should begin with 3 breaths of Tyvaso (18 mcg of treprostinil), per treatment session, 4 times daily.” This equates to 6 mcg of treprostinil per breath, and a total daily dose of 72 mcg of treprostinil. (*Id.*)

105. The maintenance dose “should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated, until the target dose of 9 breaths (54 mcg of treprostinil) is reached per treatment session, 4 times daily.” (*Id.*)

106. According to the 2009 Tyvaso® Label, “[t]he maximum recommended dosage is 9 breaths per treatment session, 4 times daily.” (*Id.*) This equates to a total daily dose of 216 mcg of treprostinil.

**B. Physicians Extensively Prescribe Inhaled Treprostinil Off-Label to Treat PH-ILD Soon After Tyvaso is Approved in 2009 to Treat PAH**

107. While Tyvaso® was not FDA-approved for PH-ILD until 2021, the idea for, and demonstrated success of, using inhaled treprostinil in Group 3 patients (including PH-ILD patients) long predates both Tyvaso®'s approval date for PH-ILD and the April 17, 2020 filing date of the '810 provisional. This is not surprising because CQ Deng, a named inventor on the '327 patent, testified that "if you focus on the pulmonary hypertension side, no matter what is underlying disease, if your drug working in the WHO Group 1, there's a reasonable assumption that probably you can test that in other WHO groups: WHO Group 2, WHO Group 3, WHO Group 4, WHO Group 5." (Deng Depo. Tr. at 23:5-24:11.) Dr. Waxman also opined that there were "lots of overlap between the various groups. When you look at the pathology," "the mediators that are circulating," "the fundamental abnormalities of proliferation and abnormal cell death," and that "it made sense, again, in my opinion, to study this drug in other forms of pulmonary hypertension." (Waxman Depo. Tr. at 50:18-51:10; *see also* DTX0140, 2017 Waxman Tr. at 3:17-4:10.) He further stated that any negative reactions to using Tyvaso® in PH-ILD patients came from "narrow minded conservative physicians" who believed "that if you deviate from the guidelines, you aren't doing the right thing." (Waxman Depo. Tr. at 226:11-17.)

108. Indeed, pulmonary hypertension physicians have often considered successful PAH treatments for use in other WHO Group populations. For example, a 2015 survey of U.S. pulmonary vascular disease centers showed that PAH therapies, including treprostinil, were used in patients with non-Group 1 PH. (DTX0058, A. W. Trammell, et al., *Use of pulmonary arterial hypertension-approved therapy in the treatment of non-group 1 pulmonary hypertension at US referral centers*, *Pulm. Circ.* 5(2):356-63 (2015) (LIQ\_PH-ILD\_00002539).) In 2017, the Giessen PH registry reported that 78% of WHO Group 3 patients, including PH-ILD patients, were on PAH

therapies. (DTX0043, H. Gall, et al., *The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups*, J. Heart Lung Transplant. 36(9):957-67 (2017) (LIQ\_PH-ILD\_00001617) at LIQ\_PH-ILD\_00001625.)

109. Some physicians began prescribing Tyvaso off-label to treat PH-ILD patients shortly after it was approved to treat PAH in 2009. Dr. Channick testified that he and his colleagues prescribed Tyvaso® to PH-ILD patients almost immediately after it was approved to treat PAH in 2009. (Anticipated testimony of Dr. Channick.) Dr. Hill also testified that he began prescribing Tyvaso® to PH-ILD patients within one year of its 2009 approval to treat PAH. (Anticipated testimony of Dr. Hill.)

110. Additionally, the steering committee members for the INCREASE study—Drs. Nathan, Tapson, and Waxman—all used inhaled treprostinil to treat PH-ILD patients prior to April 2020. Dr. Nathan testified to this effect. (Anticipated testimony of Dr. Nathan.)

111. Dr. Tapson confirmed that he used Tyvaso to treat patients with PH-ILD in his time at Duke University Medical Center and at Cedars Sinai. (Tapson Depo. Tr. at 43:16-44:21 (discussing Tyvaso use for PH-ILD patients at Duke), 52:5-23 (discussing Tyvaso use for PH-ILD patients at Cedars Sinai).) Dr. Tapson testified that he began treating PH-ILD patients with Tyvaso® as early as 2009:

Q: When Tyvaso® was approved, did you start using it for your patients?

A: To some degree, yes.

Q: And what type of patients would you use Tyvaso® for?

A: Patients with Group 1 disease, for example, who were ill enough for a prostanoid but not deemed ill enough for a parenteral drug. Or sometimes a Group 3 patient, for example, who might have severe pulmonary hypertension associated with ILD.

(*Id.* at 40:5-1, *see also id.* at 160:20-164:18.)

112. When asked if the PH-ILD patients he treated at Duke benefited from using Tyvaso®, Dr. Tapson testified “some seemed to benefit, yes.” (*Id.* at 43:8-14.) He also testified that at Duke, “there were other physicians treating PH that did treat this in certain circumstances when these kind of cases came along,” referring to treating PH-ILD patients with Tyvaso®. (*Id.* at 43:16- 44:4.) Dr. Tapson began work at Cedars Sinai in 2014, and testified that, while there, he continued in “selected patients with Group 3 disease we would use Tyvaso®.” (*Id.* at 52:5-12.)

113. Dr. Tapson similarly testified that he treated PH-ILD patients with Tyvaso during his tenure at Duke University Medical Center and Cedars-Sinai Medical Center, and that his patients showed improvement after Tyvaso treatment:

Q. And so then, it would be a correct statement that you, in fact, during your time at Cedars, prior to INCREASE, prescribe Tyvaso to treat PH-ILD patients?

A. I did do that, yes.

Q. And I understand that some patients benefited, some patients didn't, some patients might have been hard to tell. But at your time at Cedars, there was some patients that did, in fact, improve their PH-ILD did, in fact, improve upon Tyvaso administration, correct?

A. Well, some were in the INCREASE study, but I don't remember how many. Yes, some did improve.

(*Id.* at 160:20-164:18 (objections omitted); *see also id.* at 40:8-21, 41:22-43:14, 46:2-48:4, 52:13-23.)

114. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

115. Dr. Waxman also testified that he treated PH-ILD patients with inhaled treprostinil prior to April 2020. (Waxman Depo. Tr. at 49:22-50:5; 46:22-47:1; *see also id.* at 25:19-26:19, 52:23-53:16, 83:11-84:13, 214:8-12, 224:16-21, 225:24-226:10.) Dr. Waxman also used Tyvaso® off-label to treat Group 3 patients (which includes PH-ILD patients) as soon as it was commercially available:

Q. In this abstract with respect to the statement we read on the retrospective assessment using inhaled treprostinil for these Group-3 patients, do you recall, did you start using inhaled treprostinil in this Group-3 patient population when it became commercially available?

A. Yes.

(*Id.* at 49:22-50:5 (objections omitted).)

He also confirmed that he used Tyvaso® in PH\_ILD patients off-label prior to its approval:

Q: . . . You used Tyvaso before it was approved in PH-ILD patients with PH-ILD, correct?

A: Yes.

(*Id.* at 214:8-12.)

116. When discussing the Agarwal 2015 abstract he co-authored (discussed in detail below), Dr. Waxman confirmed that the Group 3 patients in the study were treated with inhaled treprostinil prior to 2014. (*Id.* at 46:22-47:1.)

117. In discussing his 2017 John Vane Presentation (discussed in more detail below), Dr. Waxman confirmed that his research group was treating more than 60 Group 3 patients with inhaled treprostinil as of 2017, and confirmed that “[i]t was a clinical decision to treat them prospectively[.]” (*Id.* at 83:1-84:13.)

118. He further testified that many of these patients saw improvements and that he continued to prescribe Tyvaso to his PH-ILD patients before its eventual FDA approval in 2021. (*Id.* at 60:1-12.) He also confirmed that he did not stop treating PH-ILD patients with Tyvaso® in light of earlier terminated studies, including those involving different forms of treprostinil, such as oral treprostinil, because of its different administration route. (*Id.* at 111:8-24.)

119. Finally, Drs. Rajan Saggar, Rajeev Saggar, and Kishan Parikh further confirmed that they and their colleagues prescribed inhaled treprostinil off-label to treat patients with PH-ILD as early as 2009. Dr. Rajan Saggar testified that, from the time Tyvaso® was approved in 2009 up until 2020, his group at UCLA treated “somewhere between 75 and 100” PH-ILD patients with Tyvaso. (Rajan Saggar Sept. 24 Depo. Tr. at 143:12-23.)

120. Dr. Rajeev Saggar testified that during his time as a practicing physician before 2018, although the Tyvaso® indication was for Group 1 PAH, “we used it frequently to treat outside that indication. In other words, we treated pulmonary hypertension, for example in PH-ILD.” (Rajeev Saggar Depo. Tr. at 49:4-11.) He further testified that he first used Tyvaso® off-label for the treatment of PH-ILD patients “around 2010” and that he prescribed the dose described in the Tyvaso label for PAH:

Q: Prior to 2014, had you been using Tyvaso off-label for treatment of PH-ILD?

A: Yes, I was.

Q: When was the first time that you can recall that you used Tyvaso off-label for treatment of PH-ILD?

A: On or around 2010.

Q: When you were using Tyvaso off-label to treat PH-ILD before its approval in PH-ILD, what was the dose that you would use in your patients?

A: Nine to 12 breaths, four times a day.

Q: So it's the same dose escalation that's described in the Tyvaso label for PAH; is that correct?

A: Yes. So at the time, Tyvaso was approved in Group 1 PAH. At the time, we believed that the molecule treprostinil would be effective to treat pulmonary hypertension, whether it's Group 1 PAH or it's Group 3 PH-ILD. And so, at that time, given the understanding of how to titrate Tyvaso nebulizer, which was limited, and based on that study, we followed the guidance of that study to help titrate the patient.

Q: Just you personally, how many PH-ILD patients do you believe you've treated off-label with Tyvaso prior to Tyvaso's approval for PH-ILD?

A: I would have to say somewhere around 80 to over 100.

(*Id.* at 222:13-223:19 (objections omitted); *see also* 202:8-203:1.)

121. And Dr. Rajan Saggar's use of Tyvaso to treat PH-ILD was in fact part of a standardized protocol at UCLA:

Q. Does UCLA have a protocol or a standard of care for PH-ILD patients that uses TYVASO for treatment of PH-ILD?

A. We believe -- yes. The answer is yes. We -- we believe that treprostinil, even prior to its approval in 2021 as an inhaled therapy for PH-ILD, we believe since 2009, 2010 that -- and we do this clinically. In our -- our standard of care at UCLA is to use treprostinil in one of its forms,

specifically inhaled or parenteral for PH-ILD. That's our -- that's our go-to first line therapy and has been since 2010.

(*Id.* at 170:23-171:11 (objections omitted); *see also* Rajan Saggar Depo. Tr. (Sept. 17, 2024) at 26:13-29:12.)

122. Dr. Rajeev Saggar further testified that his brother, Dr. Rajan Saggar treated PH-ILD patients with Tyvaso prior to 2020, in addition to the physicians David Ross, John Belperio, Richard Channick, Jeremy Feldman, Shelley Shapiro, Aaron Waxman, Victor Tapson, Paul Forfia, and Angeli Vavia. (*Id.* at 225:14-226:8.)

123. Dr. Rajan Saggar also testified that he used treprostinil to treat patients with PH-ILD as early as 2009, stating “once the inhaled product was approved through Group 1 PAH in 2009, we started to use inhaled therapy for PH-ILD, specifically Tyvaso®.” (Rajan Saggar Sept. 17, 2024 Depo. Tr. at 20:17-21:18, 27:8-24.) Even prior to 2009, Dr. Rajan Saggar testified that he used Remodulin, intravenous treprostinil, as early as 2005. (*Id.* at 22:1-23:23.) He further estimated that while he was at UCLA, his group probably treated between 75 and 100 PH-ILD patients with Tyvaso between 2009 and 2020. (*Id.* at 143:12-23.)

124. An internal UTC email further confirms Drs. Rajan and Rajeev Saggar’s use of inhaled treprostinil to treat PH-ILD patients more than one year before the ’327 patent’s priority date. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

125. Dr. Parikh, another clinician and the author of Parikh 2016, also testified that he, and other clinicians at Duke, treated patients with PH-ILD using Tyvaso® prior to 2020:



Q: Okay. Were you involved in the care of patients . . . who received TYVASO who had PH-ILD during the time period 2013 to 2018?

A: Sure, yes.

(Parikh Depo. Tr. at 25:6-11.)

[REDACTED]

(*Id.* at 33:8-14 (objection omitted).)

126. As discussed further below in Section V.C.4 Dr. Parikh's 2016 publication corroborates his testimony that PH-ILD patients were indeed treated using inhaled treprostinil at the Duke University Medical Center. (DTX0354, K. Parikh., et al., Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension, *J. Cardiovasc. Pharmacol.* 67(4); 322–25 (2016) (“Parikh 2016”) (UTC\_PH-ILD\_010599); *see also* Parikh Depo. Tr. at 23:11-25:11, 26:24-27:4, 25:6-11, 32:3-18, 33:1-34:9, 34:23- 35:1, 47:10-49:14, 66:7-67:16, 81:5-84:16.)

127. Drs. Channick and Hill further testified that they and their colleagues followed the 2009 Tyvaso label's dosing regimen when prescribing Tyvaso off-label to PH-ILD patients. (Anticipated testimony of Dr. Channick; Anticipated testimony of Dr. Hill.) Drs. Waxman, Rajan and Rajeev Saggar, Kishan Parikh, and Victor Tapson similarly testified that their off-label use of inhaled treprostinil to treat PH-ILD patients followed the dosing regimen disclosed in the 2009 Tyvaso label. (*See* Waxman Depo. Tr. at 57:19-59:4 (regarding Agarwal 2015: Did you follow the Tyvaso dosing regimen when using inhaled . . . when using Tyvaso in this study? A: Yes.” (objection omitted)), 81:15-83:4, 97:7-99:15, 130:16-131:14, 165:20-167:15, 167:20-169:14, 200:25-205:25; *see also* Rajan Saggar Depo. Tr. (Nov. 20, 2024) at 204:25-205:8; Rajeev Saggar

Depo. Tr. at 222:20-223:19; Tapson Depo. Tr. at 46:2-9; Parikh 46:21-47:15 (Q: [REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED].”).)

128. Dr. Waxman testified that his prior use of inhaled treprostinil in Agarwal 2015 which included the treatment of PH-ILD patients, followed the dosing regimen disclosed in the Tyvaso label:

Q. Did you follow the Tyvaso dosing regimen ... when using Tyvaso in this study?

A. Yes.

Q. And increased to goal of 9 to 12 breaths four times daily -- I'm sorry. Let me back up. The three breaths four times daily, that's the initial dosing for Tyvaso, correct?

A. Correct.

Q. And then as the patients tolerate that, you titrate up to more breaths?

A. Yes.

Q. And in that more breaths, is that reflective of the 9 to 12 breaths four times daily?

A. It is, yes.

Q. Is that considered the maintenance dosing for Tyvaso?

A. I would call it the standard goal, FDA-approved dosing.

Q. Of Tyvaso?

A. Yes.

Q. Each breath of Tyvaso you recall is six micrograms of treprostinil per breath?

A. Yes.

Q. And so three breaths would be 18 micrograms of treprostinil?

A. Yes.

Q. And that's what the patients were started on in this study?

A. Yes.

Q. And nine breaths would be about 54 micrograms of treprostinil on this standard goal?

A. Yes.

(Waxman Depo. Tr. at 57:19-59:4 (objections omitted); *see also id.* at 81:15-83:4, 97:7-99:15, 130:16-131:14, 165:20-167:15, 167:20-169:14, 200:25-205:25.)

129. When discussing Faria-Urbina 2018, Dr. Waxman explained that they used the “usual Tyvaso® dosing” to treat PH-ILD patients:

Q: If you look at Treatment Regimen and Follow-Up, it indicates that the patients received inhaled treprostinil at 3 breaths 18 micrograms four times daily, 72 micrograms per day. Do you see that?

A: Yes.

Q: That's the usual Tyvaso dosing you talked about during your talk?

A: Based on Group-1.

Q: So you used Group-1 dosing from the FDA-approved Tyvaso label in Group-3 patients?

A: Initially, yes.

Q: Why did you start with the -- why did you use Group-1 dosing recommendations for Group-3 patients?

A: Because that's what we knew.

Q: Knew based on experience with pulmonary arterial hypertension Group-1?

A: And just experience with the drug.

(Waxman Depo. Tr. at 97:7-98:1.)

130. Dr. Rajan Saggar also confirmed that he administered inhaled treprostinil consistent with the dosing regimen in the 2009 Tyvaso® label:

Q. Do you know what dose of TYVASO you were using off label for treatment of PH-ILD?

A. Yeah. So in those days, we were limited -- or at least the literature was limited, you know, to nine breaths four times a day. Perhaps up to 12 breaths four times a day. But most of us weren't pushing it past that dose.

(Rajan Saggar Nov. 20 Depo. Tr. at 204:25-205:8 (objections omitted).)

131. Dr. Rajeev Saggar provided similar testimony confirming that he also used the 2009 Tyvaso® Label dosing regimen. (*See* paragraph 120 above.)

132. Dr. Parikh also confirmed that, concerning his 2016 publication, Parikh 2016 (*see* Section V.C.4, physicians at Duke University Medical Center adhered to the 2009 Tyvaso label's dosing regimen when using Tyvaso to treat patients with PH-ILD:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Q. So all the patients that are reported in this paper in this study received at least the approved dosage for TYVASO, which was 54 micrograms per single-event dosing session, correct?

A. No. There were people that did not -- that couldn't tolerate it, right? There's a percentage of patients that were not able to.

Q. So if you look at the Tolerability section, and that's on the second column of that page.

A. Yes.

Q. So it says "Tolerability of the total cohort," and the total cohort was 80 patients, correct?

A. Yes.

Q. So 78 of those 80 patients were actually dosed with TYVASO to 12 breaths, 72 micrograms four times daily, correct?

A. Yes, yes.

Q. So that means at a minimum, at least those 78 patients received up to the approved dose of nine breaths, 54 micrograms four times daily, correct?

A. That is correct.

(Parikh Depo. Tr. at 47:10-49:14 (objections omitted).)

133. Dr. Tapson similarly testified that he used the same 2009 Tyvaso label dosing to treat PH-ILD patients more than one year before the '327 patent's priority date. (Tapson Depo. Tr. at 46:2-9.)

134. Drs. Channick and Hill went on to testify that they and their colleagues observed improved exercise capacity (as measured by 6MWD and NYHA functional class), as well as improved NT-proBNP levels in the PH-ILD patients they treated off-label with Tyvaso.

(Anticipated testimony of Dr. Channick; Anticipated testimony of Dr. Hill.) Drs. Waxman, Rajan and Rajeev Saggar, Victor Tapson, and Kishan Parikh observed similar clinical outcomes.

135. In 2017, Dr. Waxman publicly stated at the John Vane Memorial Symposium that PH-ILD patients treated with the 2009 Tyvaso dosing regimen “had upwards of a 65-meter improvement” in six-minute walk distance. (DTX0140, 2017 Waxman Tr. at 13:20-21; *see also* Waxman Depo. Tr. at 31:21-34:23, 59:22-60:12, 62:18-64:20, 86:22-88:13, 90:4-91:5, 109:4-16, 112:10-114:9, 115:15-116:18, 117:1-6, 176:10-19, 183:5-14, 195:6-198:2.) He also testified that the majority of the patients he discussed at the John Vane Memorial Symposium got better with inhaled treprostinil therapy:

Q: You'd agree that the vast majority of those 60 patients got better with the inhaled treprostinil therapy?

A: Yes

(Waxman Depo. Tr. at 90:15-19 (objections omitted).)

136. Dr. Rajan Saggar also testified that he saw improvements in 6MWD, NT-proBNP levels, and FVC in the PH-ILD patients that he treated with Tyvaso:

Q. You've mentioned that you've used inhaled TYVASO for treatment of PH-ILD patients; correct?

A. Correct.

Q. And have you seen improvements in, for example, six-minute walk distance in those patients?

A. Yes.

Q. Have you seen improvements in NT-proBNP levels in those patients?

A. Yes.

(Rajan Saggar Sep. 24 Depo. Tr. at 33:9-21 (objections removed); *see also id.* at 46:22-49:21, 178:2-179:15; *see also* Rajan Saggar Nov. 29 Depo. Tr. at 190:9-22, 192:7-24.)

137. Additionally, Dr. Rajan Saggar testified that he was not surprised by the results of the INCREASE Study when they came out because physicians were already seeing improvements in exercise capacity based on their own clinical practice:

Q: Given your -- your experience that we have talked about today, were you surprised that treatment of PH-ILD patients with TYVASO resulted in significant improvements in exercise capacity based on six-minute walk distance?

A: No.

Q: Why not?

A: I mean, we've already -- we've already seen this in our own clinical practice.

(Rajan Saggar Depo. Tr. at 178:2-14 (objections omitted).)

138. Dr. Rajeev Saggar provided similar testimony. (*See* Rajeev Saggar Depo. Tr. at 59:12-20, 81:15-82:11, 202:8-203:1, 222:13-223:12, 223:14-223:19, 224:16-226:8, 234:17-235:17.) As did Dr. Tapson. (*See* Tapson Depo. Tr. at 160:20-164:18 (objections omitted); *see also id.* at 40:5-21, 41:22-43:14, 44:22-45:14, 45:18-48:21, 49:4-21, 50:8-16, 52:5-23, 53:24-54:5, 63:23-64:25, 65:11-20, 66:6-12, 68:23-69:4, 138:20-139:18, 160:20-161:21, 161:23-163:4, 163:15-164:7, 164:9-18.) Dr. Parikh further testified that the patients in his 2016 study experienced an increase in six-minute walk distance and [REDACTED]:

Q. If you look at the next sentence in the Efficacy Parameters section -- Do you see that?

A. Yes.

Q. It says: "The average change in six-minute walk distance was 3.9 meters (95 percent confidence interval minus: 13.4, 21.2) from baseline to follow-up." Do you see that?

A. Yes.

Q. So does that indicate that the average improvement of the 80 patients in this study for six-minute walk distance from baseline to the first follow-up appointment was an improvement of 3.9 meters?

A. Yes.

Q. And then it goes on to indicate that the average improvement of the 80 patients in this study from baseline to the second follow-up was 31.6-meter improvement in their six-minute walk distance, correct?

A. Correct.

[REDACTED]

(Parikh Depo. Tr. at 66:7-67:16 (objections omitted); *see also* DTX0354, K. Parikh., et al., Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension, *J. Cardiovasc. Pharmacol.* 67(4); 322–25 (2016) (“Parikh 2016”) (UTC\_PH-ILD\_010599 at -603).)

139. The physicians identified above used commercially available Tyvaso® to treat their PH-ILD patients and were able to have the drug covered by insurance. (*See e.g.*, Anticipated testimony of Drs. Hill and Channick.) Dr. Waxman testified to this effect:

Q. How do the patients in this study get their insurance companies to pay for the Tyvaso?

A. We would use the terminology “out of proportion.”

Q. And what would be out of proportion?

A. The pulmonary hypertension.

Q. Would you say out of proportion to ILD or just PH out of proportion?

A. Out of proportion to any other underlying disease.



Q. So if they had interstitial lung disease, you would write it as pulmonary hypertension out of proportion of interstitial lung disease?

A. Yes.

Q. And if it was COPD, PH out of proportion to COPD?

A. Yes.

Q. And that would be submitted for the insurer to get reimbursed, the patient reimbursed or have their Tyvaso paid for?

A. Correct.

(Waxman Depo. Tr. at 67:12-68:10; *see also id.* at 214:8-16.)

140. After prescribing Tyvaso to a PH-ILD patient, nurses provided through specialty pharmacies would instruct the patients on how to use the Tyvaso inhalation device and the dosing regimen approved for PAH. (Anticipated testimony of Drs. Hill and Channick.) Dr. Hill and his colleagues would also discuss the proper administration of Tyvaso with patients during in-person visits. (Anticipated testimony of Drs. Hill and Channick.)

141. From 2014 to 2018, UTC's drug safety reports from the FDA Adverse Events Reporting System (FAERS) Public Dashboard document at least four instances of physicians' off-label use of Tyvaso to treat PH-ILD patients. (DTX0175, FDA Adverse Event Reporting System (available at <https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/6b5a135f-f451-45be-893d-20aaec34e28e/state/analysis>) (LIQ\_PH-ILD\_00148745); *see also* Bunce Depo. Tr. at 22:15-25, 20:25-21:14.) [REDACTED]

[REDACTED] (Bunce Depo. Tr. at 20:25-21:14.) And Dr. Martine Rothblatt, UTC's Chairman and CEO, confirmed that Dr. Waxman (among other physicians) used Tyvaso to treat PH-ILD patients prior to UTC's May 2, 2018 Q1 2018 earnings call and that such use was paid for by "payors":

[S]tarting with the COPD *and* ILD. ***Treprostinil, Tyvaso is not on label for patients with these indications.*** And as you would expect, it's not an inexpensive therapy, and patients don't just, like, blindly push the pay button on Tyvaso. ***Every patient is carefully assessed by payers in ensuring that it's an appropriate patient that they're obligated to pay for and not an experimental patient.*** Having said that, both through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit, there were unmistakable signals the some of the leading physicians in this field. ***I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, "This drug works." In fact, they believe that this drug works even better in that indication than in the Group I indication in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved.***

(DTX0003, LIQ\_PH-ILD\_00000001 at -009 ("UTC 2018 Earnings Call") (emphasis added).) Dr.

Rothblatt went on to confirm that insurance companies covered PH-ILD patients' off-label use of Tyvaso, publicly stating to investors, in relevant part, that

in supporting investigator-sponsored studies and through the ***kindness and generosity of certain payers around the country*** who have gone ahead and upon the initiative of their physicians, ***were able to enable some WHO Group III patients to benefit*** [from Tyvaso and], there were unmistakable signals the some of the leading physicians in the field[,] I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, ***"This drug works."***

(*Id.* at LIQ\_PH-ILD\_00000010 (emphasis added).)

### **C. The Scientific Community Supports the Use of Inhaled Treprostinil to Treat PH-ILD**

142. In addition to treating PH-ILD patients with inhaled treprostinil, researchers and physicians began publishing on the use of intravenous and inhaled treprostinil for the treatment of PH-ILD as early as 2013.

143. Multiple studies reported positive results using treprostinil in WHO Group 3 patients, including those with PH-ILD. For example, in a 2009 study supported by a UTC research grant, Saggart, et al. reported that a patient administered parenteral treprostinil (Remodulin®)

showed improvement in the 6MWD, WHO functional class, BNP level, quality of life survey score, Borg Dyspnea Scale, and spirometric function, including an improvement in FVC. (DTX0066, R. Saggar, et al., *Treprostinil to Reverse Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis as a Bridge to Single-Lung Transplantation*, J. Heart and Lung Transplant., 28:964-7 (2009) (LIQ\_PH-ILD\_00002986) (“Saggar 2009”) at LIQ\_PH-ILD\_00002988.) In 2011, Schirro and Waxman described that inhaled treprostinil, delivered according to the “usual protocol starting with three breaths four times a day,” in patients with PH and parenchymal lung disease (a form of Group 3 PH) showed improvements in the 6MWD and on the Borg Dyspnea Scale. (DTX0055, A. Schirro and A. Waxman, *Inhaled treprostinil therapy in patients with pulmonary hypertension and parenchymal lung disease*, Eur. Respir. J., 38:2385 (2011) (LIQ\_PH-ILD\_00002474) (“Schirro and Waxman 2011”) at Abstract; *see also* DTX0054, Eur. Respir. J., Vol. 38 Suppl. 55 Table of Contents (LIQ\_PH-ILD\_00002462).) The authors concluded that inhaled treprostinil “may offer an effective and well tolerated treatment in subjects with PLD and shortness of breath exacerbated by PH.” (Schirro and Waxman 2011 at Abstract.)

# **1. Wade 200**

144. U.S. Patent App. Publication No. 2013/0096200 A1 (“Wade 200”) is a published patent application. Wade 200 is entitled “Treprostinil Treatment for Interstitial Lung Disease and Asthma,” and is assigned to UTC. (DTX0361, Wade 200 at Cover.) Wade 200 was published on April 18, 2013. (*Id.*) The named inventors are Michael Wade, Stuart Rich, Eugene Sullivan, Robert Roscigno, and Roger Jeffs. (*Id.*)

145. Wade 200 discloses the use of treprostinil for the treatment of ILD or a condition associated with ILD, including pulmonary hypertension. (DTX0361, Wade 200 at Claim 1; *see also* Wade Depo. Tr. at 35:15-25.) Specifically, Wade 200 claims a “method for treating a condition associated with an interstitial lung disease, comprising parenteral administration to a

subject in need thereof an effective amount of treprostinil, or a pharmaceutically acceptable salt thereof, wherein said condition is a pulmonary hypertension, which a complication of said interstitial lung disease.” (DTX0361, Wade 200 at Claim 1.) Further, Wade 200 in paragraphs [0082]-[0087] makes clear that *UTC* and the inventors tell POSAs that treprostinil will be used in “patients with idiopathic pulmonary fibrosis and pulmonary hypertension[,]” which is PH-ILD, a number of endpoints will be measured, including 6MWD, FVC (using a spirometer), dyspnea using the Borg scale, HRCT, and BNP, and that “[s]ubjects receiving Treprostinil *will show improvement* in the studied criteria indicating the positive effect of treprostinil treatment in patients with idiopathic pulmonary fibrosis and pulmonary hypertension.” (*Id.* at [0082]-[0087] (emphasis added).)

146. Wade 200 includes claims covering the use of inhaled treprostinil to treat PH-ILD:

- |   |
|---|
| <p>1. A method for treating or preventing a condition associated with pulmonary fibrosis, comprising administration to a subject in need thereof an effective amount of Treprostinil or its derivative, or a pharmaceutically acceptable salt thereof.</p> <p>2. The method of claim 1, wherein said derivative is an acid derivative of Treprostinil, a pro-drug of Treprostinil, a sustained release form of Treprostinil, an inhaled form of Treprostinil, an oral form of Treprostinil, a polymorph of Treprostinil or an isomer of Treprostinil.</p> |
|---|

(DTX0361, Wade 200 at Claims 1-2.)

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| <p>9. The method of claim 1, wherein said administration is performed by inhalation.</p> |
|--|

(*Id.* at Claim 9.)

147. The specification further describes the therapeutic potential of treprostinil for improving lung function and addressing disease progression in patients with conditions such as idiopathic pulmonary fibrosis (“IPF”) and PH-ILD. Wade further discloses the use of inhaled treprostinil. (*Id.* at [0012], [0020]; Wade Depo. Tr. at 36:19-22; 38:12-1.)

maceutically acceptable salt thereof. The derivative may be an acid derivative of Treprostinil, a pro-drug of Treprostinil, a sustained release form of Treprostinil, an inhaled form of Treprostinil, an oral form of Treprostinil, a polymorph of Treprostinil or an isomer of Treprostinil. In another embodi-

(DTX0361, Wade 200 at [0012].)

**[0020]** The present invention relates to methods for treating and/or preventing interstitial lung disease or asthma, or a condition associated with interstitial lung disease or asthma, comprising administering to a subject in need thereof an effective amount of Treprostinil and/or a derivative thereof and/or a pharmaceutically acceptable salt thereof. Suitable derivatives include acid derivatives, pro-drugs, sustained

release forms, inhaled forms and oral forms of Treprostinil, including those disclosed in U.S. Pat. Nos. 6,521,212 and 6,756,033 to Cloutier et. al. and US patent application publications Nos. 20050085540 and 20050282901 to Phares et. al.

(*Id.* at [0020].)

148. Example 5 provides the effects of treprostinil on biomarkers associated with pulmonary disease, including the results of a 12-week trial conducted with 44 patients with PAH who received intravenous treprostinil. (DTX0361, Wade 200 at [0076-0081].) The results showed that patients experienced a “93.0 meter median improvement in the six-minute walk.” (*Id.* at [0077].) It also disclosed a significantly improved combined ranking of 6 MW/Borg Score Index ( $p=0.0023$ ), Borg Dyspnea score (2.0 median improvement over placebo,  $p=0.23$ ), and other confirmatory efficacy endpoints.” (*Id.*)

149. In Example 6, Wade 200 further discloses a study investigating the effects of intravenous treprostinil in patients with IPF and PH. (*Id.* at [0082].) The study assessed several

endpoints, including improvements in 6MWD, FVC, and hemodynamic parameters. (*Id.* at [0082–0087].) Wade 200 concluded that intravenous treprostinil was effective in treating patients with IPF and PH. (*Id.*)

## **2. Saggar 2014**

150. In 2009, Dr. Rajan Saggar, authored an article titled “Treprostinil to Reverse Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis as a Bridge to Single-Lung Transplantation” (“Saggar 2009”). (DTX0066, R. Saggar, et al., *Treprostinil to Reverse Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis as a Bridge to Single-Lung Transplantation*, J. Heart and Lung Transplant. 28:964-67 (2009) (LIQ\_PH-ILD\_00002986) (“Saggar 2009”) at LIQ\_PH-ILD\_00002987.) The Saggar 2009 study, which was funded by UTC research grant, is a case study of one patient intended to highlight the possible efficacy of systemic prostanoid therapy, using intravenous treprostinil for PH in the setting of UIP/IPF (PH-IPF), a subset of PH-ILD. The authors reported that parenteral treprostinil improved a patient’s 6MWD, WHO functional class, BNP level, quality of life survey score, Borg Dyspnea Scale, and spirometric function, including an improvement in FVC. (*Id.*) Saggar 2009 concludes: “This case report suggests that treprostinil is a potential therapeutic option for PH-IPF.” (*Id.* at LIQ\_PH-ILD\_00002986.)

151. In 2014, Saggar et al authored an article titled “Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis,” published on pages 123–129 of volume 69 of Thorax in 2014. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000226.)

152. In Saggar 2014, the authors report on the administration of parenteral treprostinil in 15 patients with PH and pulmonary fibrosis. (*Id.* at Abstract.) Saggar 2014 reports on 6MWD



and Forced Vital Capacity (“FVC”) and haemodynamics. Patients showed “significant improvements in right heart haemodynamics” as well as “6MWD improvements following 12 weeks of parenteral treprostinil therapy (mean 59 m;  $p < 0.001$ ),” Results similar to those seen in Faria-Urbina 2018 and the ’793 patent. (*Id.* at LIQ\_PH-ILD\_00000229.)

153. The authors also reported a change in FVC percent predicted from 62% at baseline to 63% after 12 weeks. (*Id.* at LIQ\_PH-ILD\_00000228 (Table 2).) With respect to the improvement in FVC, 20 mL of lung volume is approximately 1–2% of lung volume. Saggar 2014 discloses a 1% improvement in FVC percent predicted. (*Id.*)

154. Dr. Rajan Saggar testified that Table 3 in the Appendix on LIQ\_PH-ILD\_00000243 shows that 10 out of the 15 patients had significant improvements in their FVCs. (Rajan Saggar Sept. 17, 2024 Depo. Tr. at 179:17-180:11.) He further testified that this confirmed his clinical experience that some PH-ILD patients would see an improvement in FVC after treatment with treprostinil. (Rajan Saggar Sept. 17, 2024 Depo. Tr. at 153:14-19.)

155. Saggar 2014 further reports on the measurements of BNP (brain natriuretic peptide), finding that patients levels fell from 558 pg/ml to 228 pg/ml after 12 weeks and a p-value of 0.004. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000230 (Table 4).) BNP and NT-proBNP are interchangeable. (Anticipated testimony of Dr. Channick; *see* DTX0086, Robert P. Frantz et al, *Baseline NT-proBNP correlates with change in 6-minute walk distance in patients with pulmonary arterial hypertension in the pivotal inhaled treprostinil study TRIUMPH-1*, 31 J. Heart & Lung Transplantation 811, 812 (2012) (available at [https://www.jhltonline.org/article/S1053-2498\(12\)01076-5/fulltext](https://www.jhltonline.org/article/S1053-2498(12)01076-5/fulltext)) (LIQ\_PH-ILD\_00101518).)

156. Finally, Saggar 2014 measured Dyspnea using the University of California, San Diego Shortness of Breath (“UCSD SOB”) questionnaire and the Borg Dyspnea Index (“BDI”)

which were measured at baseline and at 12 weeks. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000227.) The authors also measured health-related quality of life using the 36-Item Short Form Health Survey (“SF-36”) which is split into a physical component (“PCS”) and a mental component (“MCS”). (*Id.*) The authors found that the patients had a statistically significant improvement in UCSD SOB and SF-36 MCS scores at the end of the study ( $p < 0.05$ ; table 3). (*Id.* at LIQ\_PH-ILD\_00000229.) UCSD SOB scores changed from 87 to 73.1 with a p-value of 0.002, patients’ SF-36 MCS scores increased from 38 to 33.2 with a p-value of 0.005. (*Id.* at Table 3.) In particular, patients responding to questions in the SF-36 reported improvements in their physical functioning, bodily pain, general health, and vitality. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000229.) While not statistically significant, patients’ SF-36 PCS scores also increased from 27.1 to 28. (*Id.*) There were no significant changes in BDI. (*Id.*)

157. Saggar 2014 concludes that “[t]his open-label study suggests that gradual initiation and chronic administration of parenteral treprostinil therapy may improve haemodynamics and right heart function without compromising systemic oxygenation in an advanced PH phenotype with RV dysfunction in the setting of PF,” that the paper’s results “require confirmation in a multi-centre, randomised study design,” and that “[f]uture studies of PH-targeted therapy for PF should focus on patients with PF with the combination of advanced PH and RV dysfunction, as these subjects may have greater capacity for benefit.” (*Id.* at LIQ\_PH-ILD\_00000231-32.) Dr. Rajan Saggar, one of the authors of this publication, testified that the publication “speaks for itself” in “suggest[ing] that treprostinil is a potential therapeutic option for PH-IPF,” which is a form of PH-ILD. (Rajan Saggar Depo. Sept. 17, 2024 Tr. at 40:7-42:3, 132:15-133:3, 165:9-15.) Dr. Rajan Saggar also testified that the publication concludes that a “more advanced [PH] phenotype is where the money is in terms of the response” and that patients with “worse pulmonary hypertension”



would be “more responsive to [treprostinil] than the people who have less pulmonary hypertension.” (*Id.* at 168:22-170:3.)

158. Drs. Rajan and Rajeev Saggar, the authors of Saggar 2014, both confirmed that they were not discouraged by the results from using treprostinil to treat PH-ILD patients and that their experience with parenteral treprostinil supported the use of inhaled treprostinil to treat patients with PH-ILD. Dr. Rajan Saggar testified that he had only had experience with parenteral treprostinil up until 2009 and that once inhaled treprostinil was available when Tyvaso® was approved in 2009, clinicians started treating PH-ILD patients with it because they already had evidence that it worked in its intravenous form. (Rajan Saggar Sep. 17, 2024 Depo. Tr. at 23:16-29:12; 68:19-22; 130:15-21.) Once treprostinil was available in an inhaled form, something that was more practical in an outpatient setting as opposed to the inpatient setting, it was a natural transition. (*Id.*) Dr. Rajan Saggar also believed that inhaled treprostinil could also be used to treat PH-ILD because “it’s the same medication. It’s the same molecule. It’s just the delivery is different” and that “[t]he inhaled version of any drug, including treprostinil, is [] part of a decades-old movement to make medications for lung disease inhaled, if possible.” (*Id.* at 29:14-25.) His testimony and actual experience evidences a POSA’s motivation to switch from parenteral treprostinil to inhaled treprostinil, with a reasonable expectation of success.

159. Dr. Rajeev Saggar, another author, also testified about the results of Saggar 2014 and noted that, while the paper did not recommend parenteral treprostinil for “routine use of PH target therapy in PAH,” he clarified that that is not “how I practiced medicine” and testified he continued to use treprostinil to treat patients. (Rajeev Saggar Depo. Tr. at 206:20-207:9.) He also stated that his experience treating the patients in this study did not change his use of treprostinil in the treatment of PH-ILD patients and would use either Remodulin or Tyvaso®. (*Id.* at 228:7-22.)

He also testified that Saggar 2014 accentuated that “treprostinil is a very effective molecule, period, for the treatment of PH” although there was still skepticism about whether parenteral was the best form of treprostinil to use. (*Id.* at 226:10-227:11.)

### **3. Agarwal 2015**

160. Agarwal is an abstract titled “Inhaled Treprostinil in Group-3 Pulmonary Hypertension” that was published in April 2015. (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508 (abstract); DTX0344, UTC\_PH-ILD\_009828 (abstract); DTX0038, LIQ\_PH-ILD\_00001400 (full article).) The authors are Drs. Manyoo Agarwal and Aaron Waxman. (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508.)

161. Agarwal 2015 discloses patients who were prospectively treated with inhaled treprostinil but retrospectively analyzed with respect to how inhaled treprostinil affects dyspnea, 6MWD, the Beck Depression Inventory (“BDI”) questionnaire, and WHO functional class (“FC”) in patients with WHO Group 3 PH, including PH-ILD. (*Id.*) Agarwal 2015 described treating 35 WHO Group-3 PH patients with inhaled treprostinil for 6 months, where 15 patients had obstructive disease, 15 had restrictive disease, and 5 had mixed obstructive/restrictive disease. (*Id.*) A POSA would have understood that the patients treated in Agarwal 2015 had PH-ILD, as POSAs recognize that patients with restrictive disease would include those with PH-ILD. (Anticipated testimony of Dr. Channick; Waxman Depo. Tr. at 12:10-20, 56:23-57:9; *see also* Nathan Depo. Tr. at 202:9-12.)

162. Agarwal 2015 utilized the standard dosing from the Tyvaso® label as of 2009. (Waxman Depo. Tr. at 57:10-23.) Patients started out receiving 3 breaths of inhaled treprostinil 4 times daily and increased to 9-12 breaths 4 times daily, as tolerated. (DTX0137, Agarwal 2015 at LIQ\_PH-ILD\_00147321; *see* Waxman Depo. Tr. at 57:10-59:12.) Using Tyvaso®, which was the

only inhaled treprostinil product available as of 2015, this means each breath delivered 6 mcg, 3 breaths delivered 18 mcg per treatment session, and 4 treatment sessions per day delivered a total of 72 mcg per day. (DTX0357, 2009 Tyvaso® label at UTC\_PH-ILD\_010693 (“Dosing and Administration”); *see* Waxman Depo. Tr. at 57:10-59:12.) At 9 breaths, a patient would receive 54 mcg per treatment session for a total of 216 mcg per day (4 treatment sessions), and at 12 breaths, a patient would receive 72 mcg of treprostinil per treatment session and a total of 288 mcg of treprostinil per day (4 treatment session). (*See* DTX0357, 2009 Tyvaso® label at UTC\_PH-ILD\_010693 (“Dosing and Administration”) and UTC\_PH-ILD\_010703; *see* Waxman Depo. Tr. at 59:8-21.)

163. Agarwal 2015 reports that 26 of the patients remained on therapy for at least 6 months, with 24 patients showing “subjective improvement.” (Waxman Depo. Tr. at 57:10-23.) Agarwal 2015 further reports that the mean change in 6MWD as “+60.85m +/- 92.60 (median change +45m,  $p = 0.0019$ ),” which demonstrated a statistically significant improvement. (DTX0137, Agarwal 2015 at LIQ\_PH-ILD\_00147321; Waxman Depo. Tr. at 57:10-23.) Additionally, mPAP in the 35 patients was  $44.37 \pm 9.80$ , signaling that the patients had mPAP levels above 20 mmHg and thus above the mPAP level for classifying patients as having PH. Agarwal 2015 reports that “24 of these pts reported subjective improvement” while median change in 6MWD was +45m,  $p = 0.0019$  and in patients with restrictive disease, 6MWD “improved” “by  $50m \pm 57$  (median +61m).” For the patients in the restrictive disease category, the 6MWD improved by 50 meters with a median of 61 meters which was higher than the change across all 22 patients. (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508; Waxman Depo. Tr. at 64:14-20.) Following 6 months of treatment, Agarwal 2015 reports that patients received inhaled treprostinil doses ranging from 6 (minimum) to 15 (maximum) breaths. (DTX0161, Agarwal 2015

at LIQ\_PH-ILD\_00148508.) Agarwal 2015 concluded that “Group-3 PH can be effectively and safely treated” with inhaled treprostinil and that “[i]nhaled [t]reprostinil may offer a well-tolerated treatment in advanced lung disease patients complicated by pulmonary vascular remodeling.” (*Id.*) Agarwal 2015 further concluded that “[a] prospective clinical trial is indicated.” (*Id.*) Based on these disclosures that 6MWD improved in these patients and did so significantly ( $p < 0.05$ ), a POSA would have understood that Agarwal 2015 discloses a method of improving exercise capacity in a patient having PH associated with interstitial lung disease. Dr. Agarwal presented Agarwal 2015 in a poster presentation and publicly presented at the International Society for Heart and Lung Transplantation 35<sup>th</sup> Annual Meeting and Scientific Sessions in Nice, France in 2015. (Waman Depo. Tr. at 16:9-17:10.)

164. On October 21, 2014, Dr. Waxman sent the Agarwal 2015 abstract to Dr. Gil Golden at UTC before it was final in order to “convince” UTC to conduct a study further evaluating inhaled treprostinil for the treatment of Group 3 patients, including PH-ILD patients. (DTX0287, A. Waxman email to Dr. Gil Golden (Oct. 21, 2014) UTC\_LIQ00161733 at UTC\_LIQ00161735; *see also* Waxman Depo. Tr. 24:3-8, 24:17-20.) Dr. Waxman confirmed that the content of the abstract did not substantively change between sending it to Dr. Golden in 2014 and its publication in 2015. (Waxman Depo. Tr. at 24:3-16.) Dr. Waxman presented the data reported in Agarwal 2015 to UTC in March 2015. (*See* Smith Depo. Tr. at 97:19-99:12, 105:9-106:7; *see* Waxman Depo. Tr. at 131:2-10, 16:9-25, 17:1-4.)

#### **4. Parikh 2016**

165. Parikh 2016 is an article titled “Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension” by Kishan S. Parikh and others, including Dr. Victor Tapson, that was published on pages 322-325 of Volume 67 Issue 4 of the *Journal of Cardiovascular Pharmacology* in 2016. (DTX0354, K. Parikh., et al., *Safety and Tolerability of*

*High-dose Inhaled Treprostinil in Pulmonary Hypertension*, J. Cardiovasc. Pharmacol. 67(4): 322–25 (2016) (“Parikh 2016”) (UTC\_PH-ILD\_010599).) The Parikh 2016 study is closely associated with UTC, which funded the database creation and analysis for the Parikh 2016 article. (*Id.* at UTC\_PH-ILD\_010603 (Acknowledgements).)

166. Parikh 2016 describes a retrospective study of 80 patients with pulmonary hypertension at the Duke University Medical Center PH Clinic. Among these patients, 25 were categorized as having Group 3 PH, 6 of which had PH-ILD. (*Id.* at UTC\_PH-ILD\_010607.) The PH clinic protocol involved an initial dosing regimen of a single administration of 3 breaths (18 mcg) per session, increasing to 6 breaths (36 mcg) in the second session. (*Id.* at UTC\_PH-ILD\_010600 (Methods, Study Population).) Doses were then titrated daily by 1 breath, based on side effects, until a maximum of 12 breaths (72 mcg) four times daily was reached. (*Id.*; *see also* Parikh Depo. Tr. at 47:10-49:25.) At least 6 mcg of treprostinil was administered per breath. The study focused on assessing the tolerability of high-dose inhaled treprostinil and included only those patients who were prescribed doses exceeding 9 breaths four times daily. (DTX0354, Parikh 2016 at UTC\_PH-ILD\_010600 (Methods, Study Population).)

167. Baseline data was collected from all 80 patients, with follow-up data collected from 49 patients at Follow-up Visit 1 and from 39 patients at Follow-up Visit 2. (*Id.* at UTC\_PH-ILD\_010601 (Results).) The study found that the average increase in the 6-minute walk distance was 3.9 meters from Baseline to Follow-up Visit 1, and 31.6 meters from Baseline to Follow-up Visit 2. (*Id.* at UTC\_PH-ILD\_010602 (Efficacy Parameters); Parikh Depo. Tr. at 66:11-67:20.) Additionally, NT-proBNP decreased by 39 ng/L at Follow-up Visit 1 and 630 ng/L at Follow-up 2. (DTX0354, Parikh 2016 at UTC\_PH-ILD\_010602 (Efficacy Parameters).) The authors concluded that high doses of inhaled treprostinil were well-tolerated, noting that there was a

“favorable safety and tolerability profile among PH WHO group 3 patients in [the] study for whom there are currently no approved therapies, and [inhaled treprostinil] may provide benefit in this patient population.” (*Id.* at UTC\_PH-ILD\_010603.)

168. Parikh 2016 expressly discloses the use of inhaled treprostinil to treat PH-ILD patients. Parikh 2016 also reflected UTC’s knowledge of off-label use of Tyvaso in PH-ILD patients. (Smith Depo. Tr. at 78:24-79:10.)

**5. 2017 Waxman Presentation at the 12<sup>th</sup> Annual John Vane Memorial Symposium**

169. On March 17, 2017, Dr. Waxman, one of the authors on Faria-Urbina 2018 (described below), presented on the topic “Is There a Therapeutic Opportunity for Prostacyclins in Patients with PH Secondary to Primary Pulmonary Disease” at the 12th John Vane Memorial Symposium on the therapeutic opportunity for the use of prostacyclin in patients with Group 3 PH, including PH-ILD. (DTX0140, (“2017 Waxman Tr.”) LIQ\_PH-ILD\_00147328 at LIQ\_PH-ILD\_00147330.) That presentation was recorded and posted publicly on Vimeo as of May 22, 2017. (DTX0138, LIQ\_PH-ILD\_00147322, (“2017 John Vane Presentation”).) Dr. Waxman confirmed that he gave this presentation and that it addressed the data later disclosed in the Faria-Urbina 2018 reference (*Id.* at 68:18-70:13, 9:98-14.)

170. During his presentation, Dr. Waxman went through the data described in the Faria-Urbina 2018 paper. (*Id.* at 68-93.) Dr. Waxman also discussed pulmonary vascular remodeling, which in his opinion, regardless of any other underlying disease, is where the pulmonary vascular disease lies. (DTX0140, 2017 Waxman Tr. at 3:18-4:10; Waxman Depo. Tr. at 71:25-72:9.) He further testified that in his opinion, “regardless of what associated diseases there are, if a patient develops pulmonary vascular disease and pulmonary hypertension, there’s overlap of the

mechanism driving the disease and if we have a drug that works in one form, we should be able to re-purpose it to another.” (Waxman Depo. Tr. at 73:9-16.)

171. Dr. Waxman stated that “treatment directed at pulmonary remodeling should potentially benefit any patient with a form of pulmonary vascular disease” and that “pathways that are active in patients with PAH are also active in patients with Group 3 and even Group 2 and Group 3 and even Group 5 [patients].” (DTX0140, 2017 Waxman Tr. at 3:4-7, 3:20-22; Waxman Depo. Tr. at 73:1-77:17.) Based on these similarities and numerous small observational studies, he “decided to prospectively treat patients and do a retrospective analysis of the data.” (DTX0140, 2017 Waxman Tr. at 7:16-9:7; *see also* Waxman Depo. Tr. at 80:6-81:10.) By “prospectively treat[ing]” these patients, he and his colleagues made the affirmative decision to administer Tyvaso® to this patient population, which included patients with PH-ILD. (DTX0140, 2017 Waxman Tr. at 9:4-6; *see also* Waxman Depo. Tr. at 81:11-83:2 (Dr. Waxman testifying that he and his colleagues based the Tyvaso® dosing in PH-ILD patients on the Tyvaso® dosing for PAH).) Dr. Waxman maintained that the Faria-Urbina 2018 provides “additional support that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered. And these findings also provide additional evidence supporting . . . larger clinical trials in patients with this form of pulmonary vascular disease.” (DTX0140, 2017 Waxman Tr. at 17:10-16.)

172. Dr. Waxman also described the dosing used to treat PH-ILD, noting that patients were “started in the usual way, on inhaled treprostinil, with starting with three breaths four times daily and increased over time to an initial goal of 9-12 [breaths].” (*Id.* at 9:16-22; *see also* Waxman Depo. Tr. at 202:3-205:5.) This dosing is consistent with the 2009 Tyvaso® label, which provides an Initial Dose of “3 breaths of Tyvaso (18 mcg of treprostinil), per treatment session, 4 times

daily” and a Maintenance Dose that is “increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated, until the target dose of 9 breaths (54 mcg of treprostinil) is reached per treatment session, 4 times daily. (DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010694; *see also* Waxman Depo. Tr. at 81:11-83:2.)

173. Dr. Waxman concluded his talk stating:

And so to finish up, hopefully, you'll agree that at least these pilot findings do provide some support -- additional support that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered. And that these findings also provide additional evidence supporting more at – larger clinical trials in patients with this form of pulmonary vascular disease.

(Waxman Depo. Tr. at 91:7-13; DTX0140, 2017 Waxman Tr. at 17:8-16.)

## **6. Faria-Urbina 2018**

174. Faria-Urbina 2018 is a publication describing a retrospective study in patients with Group 3 PH, including PH-ILD, treated with inhaled treprostinil titled “Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease.” Faria-Urbina 2018 was authored by Mariana Faria-Urbina, Rudolf K.F. Oliveira, Manyoo Agarwal, and Aaron B. Waxman and it was published in 2018 on pages 139–146 in volume 196 of the journal *Lung*. (DTX0348, M. Faria-Urbina, et al., *Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease*, *Lung*, 196:139–146 (2018) (“Faria-Urbina 2018”) (UTC\_PH-ILD\_009936).)

175. Faria-Urbina 2018 describes a retrospective study in patients with Group 3 PH, including ILD, who were treated with inhaled treprostinil. (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937 (Treatment regimen and follow-up).) The results of Faria-Urbina 2018 showed “improved (or maintained) functional class[.]” “19 improved SpO<sub>2</sub>; 10 had follow-up with 6MWT—all of them showing improvement in distance walked[.]” (*Id.* at UTC\_PH-ILD\_009939.) On the basis of the data, the study concludes that “patients with Group 3 PH treated with [inhaled



treprostinil], therapy with [inhaled treprostinil] significantly improved WHO-FC and 6MWT distance” (*id.* (Discussion)) and “the results suggest that [inhaled treprostinil] is safe in patients with Group 3 PH and evidence of pulmonary vascular remodeling in terms of functional class, gas exchange, and exercise capacity.” (*Id.* at UTC\_PH-ILD\_009936 (Abstract, Conclusions).) Based on the results, the authors concluded that inhaled treprostinil was safe in Group 3 PH patients and showed evidence of improving exercise capacity in those patients. (*Id.*)

176. More specifically, Faria-Urbina 2018 describes a study in which 72 patients were treated with inhaled treprostinil at the Pulmonary Vascular Disease (PVD) Clinic at Brigham and Women’s Hospital from December 2009 to November 2016. (*Id.* at UTC\_PH-ILD\_009937 (Introduction).) Out of the 72 patients receiving inhaled treprostinil, 61 had lung disease. Out of those 61 patients, 39 were excluded due to various factors including recent hospitalizations due to unstable lung disease, the use of other PH-specific drugs within three months of starting inhaled treprostinil and missing clinical baseline data. (*Id.* at UTC\_PH-ILD\_009938 (Baseline Characteristics).) The final study population contained 22 Group 3 PH patients. (*See id.* at UTC\_PH-ILD\_009936 (Abstract).) Among the patients, nine were classified as having PH-ILD, and across all patients the mPAP, PAWP, and PVR were  $44\pm 10$  mmHg,  $10\pm 4$  mmHg, and  $8.1\pm 3.6$  WU respectively. (*Id.* at UTC\_PH-ILD\_009938 (Baseline Characteristics).) Patients were then monitored for at least three months while on inhaled treprostinil. (*Id.* at UTC\_PH-ILD\_009937 (Introduction).)

177. Faria-Urbina 2018 states that dosing with inhaled treprostinil started at three breaths (18 µg) four times daily (72 µg) with “doses [] increased as tolerated by three additional breaths (18 µg) per dosing session every 3–7 days to achieve a dose of at least 9–12 breaths or more ( $\geq 54$  µg) four times daily . . . .” (*Id.* at UTC\_PH-ILD\_009937 (Treatment regimen and follow-up).)

Dr. Faria-Urbina confirmed that PH-ILD patients (Faria-Urbina Depo. Tr. at 115:5-8) received at least 18 micrograms of inhaled treprostinil four times a day, (*see id.* at 117:4-9) which amounted to 6 micrograms per breath (18 micrograms for every three breaths). (*See id.* at 117:23-118:1.) Dr. Faria-Urbina further testified that this dose could be increased to 9 to 12 breaths (or more) in a single administration, four times daily. (*See id.* at 119:13-21.) Dr. Nathan, UTC's expert, confirmed that the dosing disclosed in Faria-Urbina 2018 falls within the scope of claim 1 of the '327 patent. (Anticipated testimony of Dr. Nathan; *see also* DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937; DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010694.)

178. This dosing scheme is substantially similar to that of the 2009 Tyvaso® Label. The initial dose in both the 2009 Tyvaso® Label and the Faria-Urbina 2018 scheme starts with 3 breaths (18 mcg) per treatment session, 4 times daily, totaling 72 mcg daily. The dose increase in the 2009 Tyvaso® Label occurs by 3 breaths at 1–2-week intervals until reaching 9 breaths (54 mcg) per session, and the Faria-Urbina 2018 scheme increases by 3 breaths every 3-7 days to achieve at least 9-12 breaths (54-72 mcg) per session. The target dose in the 2009 Tyvaso® Label is 9 breaths (54 mcg) per session, 4 times daily, totaling 216 mcg daily, whereas the Faria-Urbina 2018 scheme aims for at least 9-12 breaths (54-72 mcg) per session, 4 times daily, totaling 216-288 mcg daily.

179. The authors of Faria-Urbina 2018 reported that 21 out of the 22 patients in the study either “improved (or maintained) functional class[.]” (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009939 (Follow-up Assessment).) They also reported that “19 improved SpO<sub>2</sub>; [and] 10 had follow-up with 6MWT—all of them showing improvement in the distance walked.” (*Id.*) Dr. Faria-Urbina confirmed that patients saw statistically significant differences in the 6-minute walk distances of PH-ILD patients who underwent treatment with inhaled treprostinil. (*See* Faria-Urbina

Depo. Tr. at 130:12-21; *see also id.* at 159:14-22.) Based on this data, the study concluded that “patients with Group 3 PH treated with [inhaled treprostinil], therapy with [inhaled treprostinil] significantly improved WHO-FC and 6MWT distance” and the results suggest that “iTRE is safe in patients with Group 3 PH and evidence of pulmonary vascular remodeling in terms of functional class, gas exchange, and exercise capacity.” (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009936 (Abstract) and UTC\_PH-ILD\_009939 (Discussion).) The authors further concluded that inhaled treprostinil was safe in Group 3 PH patients and showed statistically significant improvements in 6MWD in those patients. (*Id.*) Specifically, the authors “observed significant improvement in functional class ( $n = 22$ , functional class III-IV 82 vs. 59%,  $p = 0.041$ ) and 6-min walk distance ( $n = 11$ ,  $243 \pm 106$  vs.  $308 \pm 109$ ;  $p = 0.022$ ), without a deleterious effect on resting peripheral oxygen saturation ( $n = 22$ ,  $92 \pm 6$  vs.  $94 \pm 4$ ;  $p = 0.014$ ).” (*Id.*)

180. Regarding her own publication, Dr. Faria-Urbina testified that the publication concluded that inhaled treprostinil is safe in Group 3 patients and that there was a statistically significant improvement in the patients’ 6-minute walk distance. (*See* Faria-Urbina Depo. Tr. at 96:1–99:23.)

181. Dr. Waxman similarly concluded in his 2017 John Vane Presentation that Faria-Urbina 2018 provides “additional support that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered. And these findings also provide additional evidence supporting . . . larger clinical trials in patients with this form of pulmonary vascular disease.”

182. Faria-Urbina 2018 also includes Supplementary Material which breaks out the data from Faria-Urbina 2018 into 4 tables. (DTX0505, Faria-Urbina 2018 Supplement (UTC\_PH-ILD\_219375).) Here, Tables S3 and S4 are the most relevant. Table S3 shows changes in clinical

indices from baseline to follow-up treatment with inhaled treprostinil in ILD patients. (*Id.* at -377.) Table S4 shows changes in clinical indices from baseline to follow-up after treatment with inhaled treprostinil in CPFE patients, which are a subset set of PH-ILD patients. (*Id.* at -378; Anticipated testimony of Drs. Channick/Hill.)

183. All three tables show changes in WHO Functional class, FVC, and the 6MWT. (DTX0505, Faria-Urbina 2018 Supplement at UTC\_PH-ILD\_219375-78.) Tables S3 and S4 describe a change in 6MWD of 21 meters (from  $312 \pm 112$  meters at baseline to  $333 \pm 130$  meters at follow-up) and 55 meters (from  $238 \pm 9$  meters at baseline to  $293 \pm 22$  meters at follow-up) respectively. (*Id.* at -377-78.) Notably, Table S4 describes a statistically significant increase in 6MWD in PH-ILD patients with CPFE, with a p-value of 0.018. (*Id.* at -378.)

184. Additionally, all three tables show that Faria-Urbina 2018 analyzed statistical significance of percent predicted FVC by comparing baseline to follow-up, *e.g.* (red annotations added):

**Table S3. Changes in clinical indices from baseline to follow-up after treatment with inhaled treprostinil in ILD patients**

	N	Baseline	Follow up	p-value
<b>Clinical assessment</b>	9			
WHO functional class I/II/III/IV <sub>2</sub> n		0/1/7/1	1/2/6/0	0.083
SpO <sub>2</sub> at rest, %		94 ± 3	95 ± 3	0.216
<b>Pulmonary function test</b>	7			
FEV <sub>1</sub> , % predicted		54 ± 23	51 ± 30	0.670
FVC, % predicted		53 ± 20	48 ± 27	0.414
FEV <sub>1</sub> /FVC, % predicted		102 ± 10	107 ± 15	0.490
<b>Echocardiography</b>	6			
TRV, m/s		3.6 ± 0.5	3.5 ± 0.5	0.359
Estimated sPAP, mmHg		55 ± 15	55 ± 19	0.965
<b>6-minute walk test</b>	3			
Distance, m		312 ± 112	333 ± 130	0.631
Final dyspnea Borg score		5 ± 1	4 ± 3	0.107
Final SpO <sub>2</sub> , %		83 ± 6	80 ± 3	0.493
<b>3-minute step test with metabolic cart</b>	6			
VE/VCO <sub>2</sub> slope		41.7 ± 15.3	44.3 ± 15.3	0.506
Δ P <sub>ET</sub> CO <sub>2</sub> , mmHg		-0.7 ± 2.1	-2.7 ± 1.8	0.030
Final SpO <sub>2</sub> , %		81 ± 4	75 ± 6	0.944

**Faria-Urbina 2018 Suppl. Materials, Table S3**

(DTX0505, Faria-Urbina 2018 Supplement (UTC\_PH-ILD\_219375) at Table S3; *see also id.* at Tables S2, S4.)

## 7. 2018 Waxman Science Day Presentation

185. In 2018, Dr. Waxman, gave a presentation at UTC’s “Science Day” on the findings of Faria-Urbina 2018. (DTX0077, A. Waxman, *The iTRE Study: Therapeutic Opportunity for Inhaled Treprostinil in Patients with PH Secondary to Primary Pulmonary Vascular Disease*, UTHR Science Day 2018 (2018) (LIQ\_PH-ILD\_00101301) (“2018 Waxman Presentation”) at

LIQ\_PH-ILD\_00101311-316; *see also* DTX0127, Thomson Reuters Streetevents Edited Transcript UTHR – United Therapeutics Corp to Host Science Day 2018, September 24, 2018 (LIQ\_PH-ILD\_00140569) (“2018 Waxman Tr.”).) This presentation bears UTC’s logo and UTC had to provide final sign-off before Dr. Waxman gave the presentation.

186. Dr. Waxman confirmed that this study contained the same information he previously presented in the 2017 John Vane Presentation, which concerned the same data in Agarwal 2015 and Faria-Urbina 2018. (Waxman Depo. Tr. at 125:23-126:8.) In that presentation, Dr. Waxman stated he believed UTC had to provide final sign-off before he presented the information, noting that 41% of Group 3 PH patients in the study had “ILD,” meaning they had PH-ILD. (DTX0077, 2018 Waxman Presentation at Slide 13; *see also* Waxman Depo. Tr. at 125:18-126:5.) He further reported that patients in the study showed an improvement in 6MWD of +65 m ( $p = 0.022$ ), meaning the change in the 6-min walk distance was statistically significant. (DTX0077, 2018 Waxman Presentation at Slides 11-16.) Dr. Waxman further stated that this study provided “preliminary evidence” of the study of inhaled treprostinil for the treatment of Group 3 patients, including PH-ILD patients. (*Id.* at Slide 16.)

## **8. ’793 Patent**

187. The ’793 patent, titled “Treprostinil Administration by Inhalation,” issued on July 21, 2020 from U.S. Application No. 16/778,662, which was filed on January 31, 2020. (DTX0002 (“’793 patent”) at Cover.)

188. Application No. 16/778,662 is a continuation of 16/536,954, filed on August 9, 2019, which is a continuation of Application No. 15/011,999, filed on February 1, 2016, now Patent No. 10,376,525, which is a division of Application No. 13/469,854, filed on May 11, 2012, now Patent No. 9,339,507, which is a division of Application No. 12/591,200, filed on November 12, 2009, now Patent No. 9,358,240, which is a continuation of Application No. 11/748,205, filed

on May 14, 2007, now abandoned. (*Id.*) The '793 patent claims priority to U.S. Provisional Application No. 60/800,016 which was filed on May 15, 2006. (*Id.*)

**a. Claim 1 of the '793 Patent**

189. The '793 patent has eight claims. Claim 1 of the '793 patent recites:

A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

('793 patent at Claim 1.)

190. In 2022, Liquidia and UTC litigated the validity of the '793 patent. *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755-RGA, D.I. 433 (D. Del. Aug. 31, 2022) (DTX0036, LIQ\_PH-ILD\_00001018). There, this Court ruled that “pulmonary hypertension” as used in the '793 patent includes all five groups of PH. (*Id.* at 41.) Accordingly, the '793 patent discloses treating all five groups of PH, including PH-ILD. The Court did so based on express disclosures of all five WHO groups in the specification. (*Id.*; '793 patent at 1:41-46.) The Federal Circuit affirmed the district court’s reading of “pulmonary hypertension” stating that “we agree with the district court that ‘treating pulmonary hypertension’ includes treating all five subgroups of pulmonary hypertension patients.” *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1368 (Fed. Cir. 2023).

191. In UTC’s Patent Owner Response submitted during an *Inter-Partes* Review of the '793 patent (“'793 POR”), UTC stated that “[t]he claimed invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension.” (DTX0007, Patent Owner Response (LIQ\_PH-ILD\_00000110) at LIQ\_PH-ILD\_00000180.) In support of this statement,

UTC attached the Tyvaso® 2021 label and stated that “[i]nhaled treprostinil is currently approved for pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease.” (*Id.*) The “currently approved” indication for PH-ILD on the Tyvaso label is: “Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (DTX0360, 2021 Tyvaso® Label at UTC\_PH-ILD\_010744 (Indications and Usage).) UTC’s patent attorney, Mr. Maebius, who was Lead Counsel in the ’793 IPR also testified that this statement conveyed that the claims of the ’793 patent cover the approved PH-ILD indication Tyvaso® label cited in the IPR response. (Maebius Depo. Tr. at 136:1-138:8.)

192. In conjunction with the ’793 POR, UTC also submitted an expert declaration from Dr. Waxman supporting the validity of the ’793 patent, who stated that “[i]nhaled treprostinil is also approved to treat a broader range of pulmonary hypertension patients than the therapeutics available at the time of the invention.” (DTX0101, Waxman IPR Decl. (LIQ\_PH-ILD\_00102032) at LIQ\_PH-ILD\_00102081, ¶ 95.)

193. UTC also submitted a letter to the FDA on February 12, 2024, acknowledging that the ’793 patent claims cover the approved Tyvaso® PH-ILD indication. (*See* DTX0028, Feb. 12, 2024, FDA Letter (LIQ\_PH-ILD\_00000847) at LIQ\_PH-ILD\_00000852; *see also* Snader Depo. Tr. at 232:11-237:2.) In the letter, UTC identified the ’793 and the ’327 patents as both covering the PH-ILD indication for Tyvaso. (DTX0028, Feb. 12, 2024, FDA Letter at LIQ\_PH-ILD\_00000852; *see also* Snader Depo. Tr. at 232:11-237:2.) Specifically, UTC stated “. . . the subsequent litigation on the patents **covering the new indication**—the ’793 patent, and U.S. Patent No. 11,826,327 (“the ’327 patent”)—did not trigger a 30-month stay because those patents were added to the Orange Book for TYVASO after the January 20, 2020 submission of the original YUTREPIA 505(b)(2) NDA.” (DTX0028, Feb. 12, 2024, FDA Letter at LIQ\_PH-ILD\_00000852



(emphasis added).) The Tyvaso label indication is “[p]ulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (DTX0360, 2021 Tyvaso® Label at UTC\_PH-ILD\_010744.) UTC’s in-house counsel, Shaun Snader, reviewed the letter before it was submitted to the FDA. (Snader Depo. Tr. at 230:23-231:9.)

194. These statements by UTC and its experts concerned the scope of the ’793 patent and thus confirmed that the ’793 patent claims a method of treating PH-ILD patients with inhaled treprostinil and improving their exercise capacity.

195. Finally, claim 1 of the ’793 patent is directed to delivering 15 mcg of treprostinil in a single administration event. Delivering 15 mcg at 1, 2, or 3 breaths, as claimed in ’793 patent claim 1, meets the “at least 6 micrograms per breath” limitation of claim 1 of the ’327 patent. (Smith Depo. Tr. at 224:19-225:4; Tapson Depo. Tr. at 46:14-48:5; Waxman Depo. Tr. at 58:18-59:1.) Dr. Nathan, UTC’s expert, confirmed that the dosing disclosed in the ’793 patent falls within the scope of claim 1 of the ’327 patent. (Anticipated testimony of Dr. Nathan.)

**b. The Dependent Claims of the ’793 Patent**

196. Claims 2–5 of the patent recite several different inhalers, including a pulsed ultrasonic nebulizer (claim 3) and a dry powder inhaler (claim 4), while claim 6 of the ’793 recites “wherein the formulation is a powder” and claim 7 discloses “wherein the powder comprises particles less than 5 micrometers in diameter.” None of the clinical examples in the ’793 patent, such as Examples 1 and 2, used a dry powder formulation or a dry powder inhaler, but instead a nebulized solution of treprostinil. (’793 patent at 8:63-18:20.)

197. The specification of the ’793 patent describes inhalation devices for administering treprostinil including pulsed nebulizers (*id.* at 12:39-41, 14:35-41, 16:23-25) and a dry powder inhaler (*id.* at 12:39-41). Example 2 of the ’793 patent states that “TRE was inhaled with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler.” (*Id.* at 12:39-41.) It further describes that

aerosol of treprostinil “was generated by a pulsed ultrasonic nebulizer (OPTINEB®, Nebutech, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause” and that “[t]he device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage.” (*Id.* at 14:36-42.) Claim 4 of the ’793 patent recites “wherein the inhalation device is a dry powder inhaler[,]” while the specification further describes that “[t]he inhalation device can be also a dry powder inhaler” and “[i]n such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.” (*Id.* at Claim 4, 7:22-26.)

198. The specification also discloses the dosage of treprostinil administered to patients. It describes that treprostinil is administered in “from about 15 µg to about 100 µg” (*id.* at 7:55-59) in “20 breaths or less” and preferably in 3, 2, or 1 breaths. (*Id.* at 7:60-64 (“Microgram,” “mcg,” and “µg” are synonymous).) A POSA would have understood that 15 µg to about 100 µg in preferably 3, 2, or 1 breaths would be anywhere from 5 µg to 100 µg per breath (i.e., 15 µg/3 breaths to 100 µg/1 breath), with this range including 6 µg per breath.

199. Table 2 of the ’793 patent reports “[e]xtremes of the relative changes of hemodynamic and gas exchange parameters” following inhaled treprostinil treatment as compared to placebo. Table 2 is reproduced below. (*Id.* at Table 2.)

Extremes of the relative changes of hemodynamic and gas exchange parameters compared to baseline after inhalation of Placebo (n = 4), 30 µg treprostinil (n = 12), 45 µg treprostinil (n = 9) and 60 µg treprostinil (n = 20). Highest (max) and lowest (min) values during the observation period are shown. Data are given as percent of baseline values (mean ± SEM).				
	Placebo	30 µg TRE	45 µg TRE	60 µg TRE
PAP (min)	99.4 ± 3.0	83.4 ± 3.2	77.6 ± 6.8	79.5 ± 2.4
PVR (min)	101.4 ± 1.9	84.4 ± 4.4	71.4 ± 8.9	77.5 ± 3.7
CO (max)	99.7 ± 1.1	108.8 ± 3.8	108.6 ± 5.6	103.8 ± 2.0
SVR (min)	104.3 ± 4.3	97.7 ± 4.2	92 ± 3.9	91.3 ± 2.1
SAP (min)	102.7 ± 1.7	97.3 ± 1.9	96.1 ± 1.5	93.6 ± 2.9
HR (max)	105 ± 2.1	106.1 ± 2.9	99.1 ± 2.4	101.1 ± 0.9
SaO2 (min)	98.2 ± 0.4	101 ± 0.3	94.4 ± 1.8	95.8 ± 0.9
SvO2 (max)	104.5 ± 1.4	102.4 ± 1.3	104.5 ± 4.4	102 ± 1.0

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; HR = heart rate; SaO2 = arterial oxygen saturation; SvO2 = central venous oxygen saturation.

200. Example 2 of the '793 patent describes three different studies of inhaled treprostinil in a total of 123 patients. (*Id.* at 12:20-27.) The characteristics of the patients across the three studies are described in Table 3 of the patent, which is reproduced here:

Patient characteristics, hemodynamic parameters and gas exchange values at baseline, before challenge with inhalative prostanoids.												
	N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn * s * cm <sup>-5</sup> ]	SAP [mmHg]	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO2 [%]	SvO2 [%]
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2	63.9 ± 2.4
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1	64.4 ± 2.3
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Group 1 corresponds to study i); randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE).  
a = 7.5 g ILO vs. 7.5 µg TRE,  
b = 7.5 g ILO vs. 15 µg TRE (6 min inhalation time),  
c = 7.5 g ILO vs. 15 µg TRE (3 min inhalation time).  
Group 2 corresponds to study ii); evaluation of maximal tolerated dose of TRE.  
a = placebo inhalation,  
b = 30 µg TRE,  
c = 60 µg TRE,  
d = 90 µg TRE,  
e = 120 µg TRE.  
Group 3 corresponds to study iii); reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 µg.  
a = 18 pulses of 100 µg/ml TRE,  
b = 9 pulses of 200 µg/ml TRE,  
c = 3 pulses of 600 µg/ml TRE,  
d = 2 pulses of 1000 µg/ml TRE,  
e = 1 pulse 2000 µg/ml TRE.  
Etiology of pulmonary hypertension was classified as idiopathic PAH (i), PAH of other causes (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).

(*Id.* at Table 3.)

201. Of note, Table 3 describes that the “[e]tiology of pulmonary hypertension” of patients in the study was “classified as idiopathic PAH (i), PAH of other causes [etiology of PH in the patients] (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).” A POSA, therefore, would have understood that pulmonary fibrosis as described in the ’793 patent is a form of PH-ILD, and that PH-ILD patients were treated in the ’793 patent examples. (Anticipated testimony of Dr. Channick; Anticipated testimony of Dr. Nathan.)

202. In study i), 44 patients with moderate to severe pre-capillary PH inhaled either 7.5 or 15 µg of treprostinil. (’793 patent at 13:36-50, Table 3.) Inhalation of treprostinil resulted in a decrease in PVR. (*Id.* at 15:7-8, 15:27-41, Fig. 7.) Study ii) describes subjects who received either 30, 60, 90, or 120 µg of inhaled treprostinil. (*Id.* at 13:51-62.) The ’793 patent reports that treprostinil inhalation led to “maximal decreases of PVR to  $76.5 \pm 4.7\%$  (30 µg),  $73.7 \pm 5.8\%$  (60 µg),  $73.3 \pm 4.3\%$  (90 µg) and  $65.4 \pm 4.1\%$  (120 µg) of baseline values” and “[c]ardiac output was increased to a maximum of  $106.8 \pm 3.2\%$  (30 µg),  $122.9 \pm 4.3\%$  (60 µg),  $114.3 \pm 4.8\%$  (90 µg) and  $111.3 \pm 3.9\%$  (120 µg TRE).” (*Id.* at 15:48-60, Figs. 8, 9.) In study iii), 48 patients inhaled one dose of treprostinil through a pulsed ultrasonic nebulizer (OPTINEB®) in either 18, 9, 3, 2, or 1 breaths. (*Id.* at 14:33-45.) Treprostinil reduced PVR in all groups while cardio output was moderately increased. (*Id.* at 16:31-41, Figs. 10, 11.)

203. Hemodynamic improvements such as significant decreases in PVR and mPAP, as shown in Table 2 of the ’793 patent, correlate with improvements in exercise capacity. The ’793 patent demonstrates that inhaled treprostinil acts as a vasodilator in patients with PH-ILD, decreasing mPAP and improving PVR. (*Id.* at 9:30-33 (concluding that the application of inhaled treprostinil was “safe, well-tolerated, and induced a strong and sustained pulmonary selective

vasodilation”), 10:59-64, 12:14-17, 12:47-50.) [REDACTED]

[REDACTED] (Smith Depo. Tr. at 167:3-168:13.) Other physicians in the field, including Drs. Tapson and Waxman, also testified that treprostinil’s effects as a vasodilator is the reason why it works in patients with PH-ILD. (Tapson Depo. Tr. at 74:16-75:21; Waxman Depo. Tr. at 73:1-16; *see also* Waxman Depo. Tr. at 36:25-42:6 (explaining hypothesis that inhaled treprostinil would work better in PH-ILD patients than systemic vasodilators because it would only vasodilate in the areas where the inhaled treprostinil is delivered).) Additionally, Dr. Waxman, on behalf of UTC, submitted a letter to the FDA indicating that inhaled treprostinil is anticipated to work in PH-ILD patients for the same reason as it does for PAH. (*See* DTX0281, Waxman Nov. 15, 2017 letter to FDA (UTC\_LIQ00104555).) The ’327 patent also confirms that this mechanism of action is present in the ’793 patent because it discloses that the way in which inhaled treprostinil affects PH-ILD patients is by promoting “direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation.” (’327 patent at 27:33-36; DTX0334, ’327 patent file history at UTC\_PH-ILD\_009463.)

**D. Dr. Waxman Convinces UTC to Pursue an Indication for Treating PH-ILD using Inhaled Treprostinil By Performing the INCREASE Study, Which Confirmed the Results of the Prior Art Studies**

**1. UTC’s Communications with Dr. Waxman**

204. On October 21, 2014, Dr. Waxman sent the Agarwal 2015 abstract to Dr. Gil Golden at UTC before it was final. (DTX0287, A. Waxman email to Dr. Gil Golden (Oct. 21, 2014) UTC\_LIQ00161733 at UTC\_LIQ00161735; *see also* Waxman Depo. Tr. at 24:3-8, 24:17-20.) When asked why he sent the abstract to UTC, Dr. Waxman testified that he was trying to “convince” UTC to conduct a study further evaluating inhaled treprostinil for the treatment of Group 3 patients, including PH-ILD patients:

Q: Were you trying to convince UTC in 2014 to use, to run a trial of Tyvaso in Group-3 patients?

A: Yes.

(Waxman Depo. Tr. at 25:19-22.)

205. Dr. Waxman confirmed that the content of the abstract did not substantively change between sending it to Dr. Golden in 2014 and its publication in 2015. (Waxman Depo. Tr. at 24:3-16.)

206. Dr. Golden replied “I love it! This is definitely the largest cohort of Group 3 PH pts Tx [(treated)] with inhaled TRE [(treprostinil)] that I have seen[,]” and upon receiving the final abstract, forwarded to UTC employees Andrew Nelson and Allison Lim. (DTX0287, UTC LIQ00161733 at UTC LIQ00161734.)

2.

207.

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

[REDACTED]


[REDACTED]

[REDACTED]

208. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3. [REDACTED]  
[REDACTED]

209. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]



210. [REDACTED]

**4. Waxman 2015 Presentation: “Inhaled Treprostinil in Group-3 Pulmonary Hypertension”**

211. A UTC slide deck dated March 9, 2015 included a presentation from Dr. Waxman’s research group at Brigham and Women’s Hospital and Harvard Medical School. (See DTX0385, (“Waxman 2015 Presentation”) UTC\_PH-ILD\_082484.) The presentation from Dr. Waxman was titled “Inhaled Treprostinil in Group-3 Pulmonary Hypertension.” (*Id.* at UTC\_PH-ILD\_082486.) The Waxman 2015 Presentation discusses a “[r]etrospective analysis of data” from “35 patients treated with iTre for 6 months,” and adds that the patients “[a]ll started on 3-breaths 4x daily and increased to a goal of 9-12 breaths 4x daily as tolerated.” (*Id.* at UTC\_PH-ILD\_082490 (highlighting added).)

### METHODS

- Retrospective analysis of data from consecutive newly diagnosed patients (incident cases) with severe symptoms, and initiated on inhaled Treprostinil
- 35 patients treated with iTre for 6 months
- Seen in the BWH PVD clinic
- All started on 3-breaths 4x daily and increased to a goal of 9-12 breaths 4x daily as tolerated
- 6-MWD, BDI, WHO FC, AE’s, dose, and subjective improvement were assessed



212. This presentation indicates that the patients in this retrospective study were treated with Tyvaso, as Tyvaso was the only inhaled treprostinil therapy on the market in 2015. The



treatment regimen is also the same as the dosing claimed in the '327 patent and encompasses the approved dosing regimen in the Tyvaso label for PAH.

213. The Waxman 2015 Presentation also adds, in the “Baseline Hemodynamics” slide, that the mean pulmonary arterial pressure, or mPAP, of the patients at baseline was  $44.37 \pm 9.80$  mmHg with the median at 45 mmHg. (*Id.* at UTC\_PH-ILD\_082493.) The patients in this retrospective study had a baseline mPAP above 24 mmHg and thus were above the mPAP needed to classify patients as having PH. (*Id.* (highlighting added).)

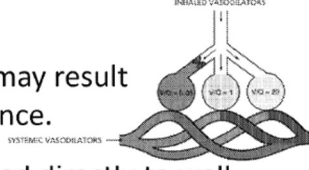
Baseline Hemodynamics		
Hemodynamics	MEAN $\pm$ SD	MEDIAN
mPAP	$44.37 \pm 9.80$	45
PCWP	$9.68 \pm 4.71$	9
CO	$4.7 \pm 1.34$	4.75
PVR	$8.77 \pm 4.76$	7.81
N=35		

BRIGHAM AND WOMEN'S HOSPITAL HARVARD MEDICAL SCHOOL

214. The Waxman 2015 Presentation also explains the motivation to pursue a study of inhaled treprostinil therapy in Group 3 PH patients. Highlighting that “[t]reatment with systemic pulmonary vasodilators may result in worsening V/Q imbalance[.]” the Waxman 2015 Presentation suggests that “[i]nhaled therapy is delivered directly to well ventilated lung units preserving V/Q[.]” (*Id.* at -489.) The Waxman 2015 Presentation also adds that inhaled therapies would have the “[p]otential for increased efficacy and decreased systemic side effects[.]” (*Id.*)

### Rational for Inhaled Therapy

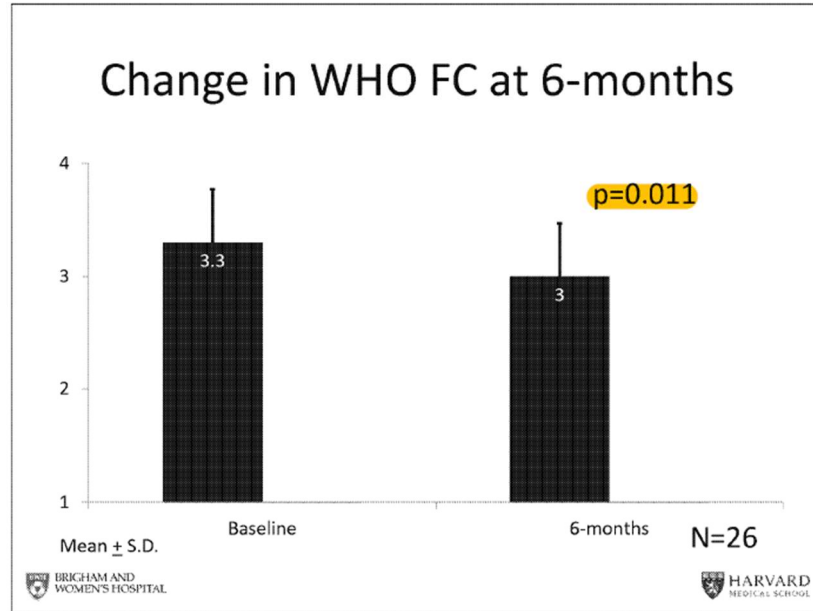
- Treatment with systemic pulmonary vasodilators may result in worsening V/Q imbalance.
- Inhaled therapy is delivered directly to well ventilated lung units preserving V/Q, and reducing undesirable alterations in perfusion
- Potential for increased efficacy and decreased systemic side effects



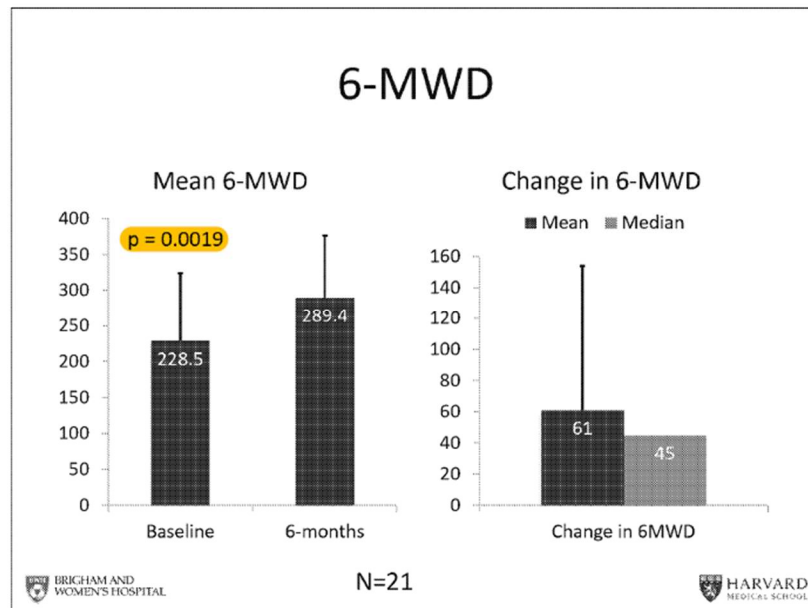
BRIGHAM AND WOMEN'S HOSPITAL HARVARD MEDICAL SCHOOL

215. V/Q mismatch or imbalance is a condition where either the ventilation of the lungs or the perfusion of the pulmonary blood vessels is impaired and thus gas exchange in the lung is imbalanced. At the time of this presentation and as explained in this slide, POSAs in the field believed that inhaled vasodilators, like Tyvaso, were less likely to cause V/Q mismatch in patients with PH-ILD than systemic vasodilators, because the inhaled treprostinil is selectively targeted to healthier areas of the lung that can participate in gas exchange. Specifically, Dr. Waxman's 2015 Presentation suggests that "[i]nhaled therapy is delivered directly to well ventilated lung units preserving V/Q, and reducing undesirable alterations in perfusion." (*Id.*) Therefore, Dr. Waxman was aware of the potential for V/Q imbalance with parenteral treprostinil, and thus conducted a retrospective study to investigate inhaled treprostinil therapy, specifically Tyvaso, in Group 3 PH patients. (*Id.*)

216. Dr. Waxman's retrospective study and the data he presented to UTC shows that he observed a statistically significant improvement in WHO functional class, a subjective assessment of a patient's exercise capacity, at six months of treatment. (*Id.* at UTC\_PH-ILD\_082498 (highlighting added).)



217. Dr. Waxman's analysis also saw a statistically significant increase in mean six-minute walk distance at six months of treatment. (*Id.* at UTC\_PH-ILD\_082501.) Therefore, Dr. Waxman's study demonstrated a statistically significant improvement in exercise ability for Group 3 PH patients, including PH-ILD patients. (*Id.* (highlighting added).)



218. The Waxman 2015 Presentation characterized these improvements as “Significant Improvement in WHO FC” and “Significant Improvement in 6-MWD[.]” (*Id.* at UTC\_PH-ILD\_082511.) Based on this data, the Waxman 2015 Presentation concluded that “[t]he findings of this pilot study provide preliminary evidence supporting the treatment of pre-capillary PAH in patients with advanced lung disease[.]” (*Id.* at UTC\_PH-ILD\_082512.)

219. Regarding the Waxman 2015 Presentation, Dr. Waxman testified that his intent in providing the abstract and presenting this data to UTC was “to convince them to do a clinical trial.” (Waxman Depo. Tr. at 128:19-129:9.) Dr. Waxman testified that, after the presentation, he recalled Roger Jeffs, President of UTC, saying that “we’re going to do this study.” (*Id.* at 131:15-132:14.) Dr. Waxman testified that the INCREASE clinical trial was the ultimate endpoint of his efforts to convince UTC to do a Phase III clinical study in this Group III, PH-ILD patient population. (*Id.*)

#### **5. FDA letter asking for orphan designation from Dr. Waxman**

220. In a November 15, 2017 letter to the FDA to support UTC’s Orphan Drug Designation application, Dr. Waxman represented to the FDA that he had been “independently involved in the development of this research concept through work that is ongoing at The Center for Pulmonary Heart Disease at the Brigham and Women’s Hospital.” (DTX0281, A. Waxman’s letter re Orphan Drug Designation to the FDA (Nov. 15, 2017) (UTC\_LIQ00104555); Waxman Depo. Tr. at 186:6-10.) Dr. Waxman further represented to the FDA that “as we have seen in our preliminary studies, it is *anticipated* that patients with ILD-PH may be more likely to benefit from prostacyclin therapy such as treprostinil.” (DTX0281, A. Waxman’s letter re Orphan Drug Designation to the FDA (Nov. 15, 2017) (UTC\_LIQ00104555) at UTC\_LIQ00104556 (emphasis added).)

221. UTC requested and approved Dr. Waxman to submit this letter to the FDA. (DTX0280, P. Smith email re Dr. Waxman's Orphan Drug Designation Letter to the FDA (Nov. 15, 2017) (UTC\_LIQ00104554).) When asked about whether UTC considered the information in Dr. Waxman's letter to be true and accurate, Dr. Smith, again in his capacity as UTC's corporate witness, stated that "[w]e believe in what he's saying here, yes." (Smith Depo. Tr. at 194:3-23.) Dr. Smith further confirmed that UTC would not submit statements it believed to be inaccurate to the FDA. (*Id.*)

## **6. 2017 Recruitment Presentation**

222. A presentation titled "Tyvaso in Pulmonary Hypertension Due to Interstitial Lung Disease (PH-ILD): The INCREASE Study ("2017 Recruitment Presentation") was provided to the INCREASE steering committee members around in 2017 to share publicly with other physicians. (DTX0384, 2017 Recruitment Presentation (UTC\_PH-ILD\_081749); *see also* DTX0383, 2017 Email (UTC\_PH-ILD\_081748); Smith Depo. Tr. at 158:11-160:6; Tapson Depo. Tr. at 130:5-131:17.) The presentation is attached to an email dated November 7, 2017 from Dr. Smith to the INCREASE steering committee including Drs. Waxman, Nathan, and Tapson. (DTX0383, 2017 Email (UTC\_PH-ILD\_081748).) In the email, Dr. Smith writes "I wanted to pass along the attached slides which could be used in any of your conversations with colleagues regarding the study background, patient populations, etc." (*Id.*) Dr. Smith confirmed in his testimony that "this slide deck would have been used for external audiences" and that there was no confidentiality designation or agreement with respect to the content in the presentation. (Smith Depo. Tr. at 177:25-178:10.) Dr. Tapson also testified that there were no restrictions on disclosing the slide deck to clinicians. (Tapson Depo. Tr. at 130:5-131:17.) The third slide of the presentation is titled "Supportive Evidence for Tyvaso in WHO Group 3 PH" referring to the data presented in Agarwal 2015. (DTX0384, 2017 Recruitment Presentation at UTC\_PH-ILD\_081752.) The following

slides discuss Dr. Waxman's data, and the "Discussion and Conclusion" slide contains the statement that "this study provides preliminary evidence supporting the safety and efficacy of inhaled treprostinil in the treatment of Group 3 PH with advanced lung disease complicated by pulmonary vascular remodeling." (*Id.* at UTC\_PH-ILD\_081755.)

## **7. 2017 INCREASE Study Protocol**

223. The '327 patent is directed to the data obtained from the INCREASE trial. (Anticipated testimony of Dr. Channick; *see also* Peterson Depo. Tr. at 159:1-14, 160:19-162:11; Deng Depo. Tr. at 97:15-98:22.) The INCREASE Study Protocol is titled "An Open-Label Extension study of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease" and was prepared with input and guidance from the INCREASE Steering Committee, including its chairman, Dr. Waxman, and UTC, [REDACTED]

[REDACTED]. The protocol reflects nothing beyond the knowledge of a POSA at the time. (Anticipated testimony of Drs Channick/Hill; *see also* Deng Depo. Tr. at 15:11-20, 138:16-139:6; Smith Depo. Tr. at 20:12-22:12; Peterson Depo. Tr. at 22:13-17, 61:23-62:17, 83:6-18.) The original protocol for the INCREASE Study is dated October 21, 2015 and the final amendment of the INCREASE study protocol is February 15, 2017. (*See* DTX0373, ("Original Protocol") UTC\_PH-ILD\_054882 and DTX0401, UTC\_PH-ILD\_105083 ("Final Protocol") (showing that the date of the final amendment of the INCREASE study protocol is February 15, 2017); Peterson Depo. Tr. at 45:5-24; Smith Depo. Tr. at 130:8-131:5.) [REDACTED]

[REDACTED] (Peterson Depo. Tr. at 45:5-24; Smith Depo. Tr. at 130:8-131:5.) In the protocol, UTC included a section titled "Rationale For Development of Study Drug in Disease/Condition" describing the rationale for treating patients with PH-ILD with inhaled treprostinil in order to improve exercise capacity. (*See* DTX0373, Original Protocol

at UTC\_PH-ILD\_054899; DTX0401, Final Protocol at UTC\_PH-ILD-105100.) This section specifies that “[i]nhaled treprostinil is expected to directly target the more ventilated portion of the lungs in patients with WHO Group 3 PH minimizing the risk of ventilation perfusion mismatch and allowing for improvements in exercise capacity.” (*Id.*) It also lists Seeger 2013, Wang 2015, Bajwa 2016, and Agarwal 2015. (*See* DTX0373, Original Protocol at UTC\_PH-ILD\_054899; DTX0401, Final Protocol at UTC\_PH-ILD-105100-01.) The data in Agarwal 2015 became part of Faria-Urbina 2018. (Waxman Depo. Tr. at 169:1-11.)

224. The 2017 INCREASE Study Description is a public disclosure of the INCREASE Study (NCT02630316) available online at [clinicaltrials.gov](https://clinicaltrials.gov), a website that provides study details for clinical studies. (DTX0008, NCT02630316: Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE (Feb. 10, 2017), available at <https://clinicaltrials.gov/study/NCT02630316?term=NCT02630316&rank=1&tab=history&a=23> (LIQ\_PH-ILD\_00000185) (“2017 INCREASE Study Description”).) The study was submitted online as early as 2015 (DTX0008, 2017 INCREASE Study Description at LIQ\_PH-ILD\_00000192 (Study Status)) and posted as version 23 on February 10, 2017. (*Id.*) The last update posted for version 23 of the 2017 INCREASE Study Description is “2017-02-10 [Actual]” and the [clinicaltrials.gov](https://clinicaltrials.gov) glossary indicates that “Last updated posted” is the “most recent date on which changes to a study record were made available on ClinicalTrials.gov.” (*Id.*; DTX0046, NCT02630316 Glossary (LIQ\_PH-ILD\_00001681) at -681.)

225. Version 23 of the INCREASE Study Description’s disclosure describes the purpose of the trial, which is “evaluate the safety and efficacy of inhaled treprostinil subjects with pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including

combined pulmonary fibrosis and emphysema (CPFE).” (DTX0008, 2017 INCREASE Study Description at LIQ\_PH-ILD\_00000193.)

226. Version 23 of the INCREASE Study Description’s disclosure contains a description of the final INCREASE clinical trial protocol including, for example, the drug product (inhaled treprostinil, i.e., Tyvaso®), dosing, inclusion/exclusion criteria for the study’s patient population, and outcome measures/endpoints. (*Id.* at LIQ\_PH-ILD\_00000192 (Study Status).) The prior art public disclosure of the INCREASE study on clinicaltrials.gov is the same as those for the final full clinical trial protocol for INCREASE, and the claims of the ’327 patent are from the data derived from the INCREASE study.

227. The 2017 INCREASE Study Description provides the details of the INCREASE Study protocol and describes the clinical study testing the safety and efficacy of inhaled treprostinil in adults PH with ILD, which is PH-ILD. (*See* DTX0008, 2017 INCREASE Study Description at LIQ\_PH-ILD\_00000185.) Specifically, the 2017 INCREASE Study Description indicates that 314 PH-ILD patients will be randomized in order to study the safety and efficacy of inhaled treprostinil. (*See id.* at LIQ\_PH-ILD\_00000193.)

228. The 2017 INCREASE Study Description describes the administration of inhaled treprostinil used in the INCREASE Study as “via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath. Inhaled four times daily and titrated up to a maximum of 12 breaths four times daily.” (*Id.* at LIQ\_PH-ILD\_00000194.) This is the same description of the drug dosage and formulation that is provided in the full final clinical trial protocol for the INCREASE study. (*See* DTX0401, UTC\_PH-ILD\_105083 at UTC\_PH-ILD\_105090; *see also* Peterson Depo. Tr. at 45:13-18; Smith Depo. Tr. at 150:10-15.)



229. The 2017 INCREASE Study Description also defines the same PH-ILD patient population that was actually studied in the INCREASE study including, for example, the inclusion and exclusion criteria used in the INCREASE study. (DTX0008, 2017 INCREASE Study Description at LIQ\_PH-ILD\_00000196-197.)

230. The inclusion criteria requirements for a patient to be diagnosed with PH include: “a right heart catheterization (RHC) within 1 year prior to randomization with the following documented parameters: a. Pulmonary vascular resistance (PVR) > 3 Wood Units (WU) and ... c. [a] mean pulmonary arterial pressure (mPAP) of  $\geq 25$  mmHg.” (DTX0401, 2017 INCREASE Protocol (UTC\_PH-ILD\_105083) at UTC\_PH-ILD\_105088.) Notably, inclusion criteria includes PH-ILD patients with “mPAP greater than or equal to 35 mmHg ... and ... a PVR greater than 4[.]” which UTC has asserted constitutes “out-of-proportion PH.” However, the exclusion criteria of the INCREASE study protocol does not exclude any patient based on elevated mPAP or PVR and therefore does not prohibit patients with PH out of proportion to ILD from taking part in the study. (DTX0401, 2017 INCREASE Protocol (UTC\_PH-ILD\_105083) at UTC\_PH-ILD\_105089-090.)

231. The 2017 INCREASE Study Description discloses all of the endpoints of the INCREASE study (as well as the asserted claims of the '327 patent). (Anticipated testimony of Dr. Channick; *Compare* DTX0008, 2017 INCREASE Study Description at LIQ\_PH-ILD\_00000194-95 (Outcome Measures), *with* '327 patent at 54:5-55:10 (all claims).) Specifically, its primary outcome measured 6MWD from baseline to week 16. (*Id.*) And its secondary outcome measures included (but were not limited to): changes in peak and trough 6MWD at weeks 12 and 15, respectively; changes in plasma NT-proBNP levels from baseline to week 16, changes in FVC from baseline to week 16, and incidence of adverse events through 16 weeks, clinical worsening,

and exacerbations of ILD. (DTX0008, 2017 INCREASE Study Description at LIQ\_PH-ILD\_00000194-195.)

**8. 2018 UTC Earnings Call with Dr. Rothblatt**

232. During a Q1 2018 UTC Earnings Call, UTC's Chairman and CEO, Dr. Martine Rothblatt, made public statements concerning the use of Tyvaso in the PH-ILD population. During the call, Dr. Rothblatt received a question regarding the rationale behind using Tyvaso in ILD. (DTX0003, UTC 2018 Earnings Call at LIQ\_PH-ILD\_00000009.) As part of her answer, Dr. Rothblatt responded:

[S]tarting with the COPD and ILD. Treprostinil, Tyvaso is not on label for patients with these indications. And as you would expect, it's not an inexpensive therapy, and patients don't just, like, blindly push the pay button on Tyvaso. Every patient is carefully assessed by payers in ensuring that it's an appropriate patient that they're obligated to pay for and not an experimental patient. Having said that, both through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit, there were unmistakable signals the some of the leading physicians in this field. ***I called out*** one of them on the call, Dr. Waxman, but there are many others, who said to UT, ***"This drug works."*** In fact, they believe that this drug works even better in that indication than in the Group I indication in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved So with that kind of data, some of which has been presented in posters and maybe even publications -- I don't know, but I've definitely seen posters, we went ahead and then had the statistics to power of the study for statistical significance, the one in the ILD population and the other in the COPD population, which are 2 distinct populations.

(*Id.* (emphasis added).) Dr. Rothblatt's statement indicates that at least Dr. Waxman, among other physicians, used Tyvaso to treat PH-ILD patients prior to the May 2, 2018 date of the earnings call. Moreover, the fact that Dr. Rothblatt states she has seen "posters" and "papers" on this issue reflects acknowledgment of Faria-Urbina 2018 and Agarwal 2015 as they speak directly to the study of Tyvaso in PH-ILD patients.

**9. February 2020 Press Release**

233. UTC's February 24, 2020 press release titled "United Therapeutics Announces INCREASE Study of Tyvaso® Meets Primary and All Secondary Endpoints," reports the findings of the INCREASE trial. (DTX0265, United Therapeutics, *United Therapeutics Announces INCREASE Study of Tyvaso® Meets Primary and All Secondary Endpoints*, <https://ir.unither.com/press-releases/2020/02-24-2020-161749814> (Feb. 24, 2020) ("Feb. 2020 Press Release") (UTC\_LIQ00063612).) The Feb. 24, 2020 Press Release specifically discloses that the INCREASE trial exhibited "Tyvaso increas[ing] six-minute walk distance by 21 meters versus placebo (p=0.0043, Hodges-Lehmann estimate) after 16 weeks of treatment." (DTX0265, Feb. 2020 Press Release.) [REDACTED]

[REDACTED] (Smith Depo. Tr. at 214:11-216:10.) The press release also reported that "[s]ignificant improvements were also observed in each of the study's secondary endpoints including reduction in the cardiac biomarker NT-proBNP, time to first clinical worsening event, change in peak 6MWD at Week 12, and change in trough 6MWD at week 15." (DTX0265, Feb. 2020 Press Release.) [REDACTED]

[REDACTED] (Smith Depo. Tr. at 215:21-216:10.) In the Press Release, Dr. Rothblatt announced that UTC achieved "highly statistically significant proof of efficacy" with the INCREASE Study. (DTX0265, Feb. 2020 Press Release.)

234. UTC's February 24, 2020 press release also specifically discloses the following:

- "INCREASE was a phase III, multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study of Tyvaso in patients with pulmonary hypertension associated with interstitial lung disease. Enrollment into the study was completed in August

2019 with a total of 326 patients. Patients were randomized in a 1:1 Tyvaso (n=163) or placebo (n=163).”

- “Secondary objectives of the study included:
  - Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
  - Time to clinical worsening calculated as the time from randomization until one of the following criteria are met:
    - Hospitalization due to a cardiopulmonary indication
    - Decrease in 6MWD >15% from Baseline directly related to disease under study, at two consecutive visits, and at least 24 hours apart
    - Death (all causes)
    - Lung transplantation
  - Change in peak 6MWD from Baseline to Week 12
  - Change in trough 6MWD from Baseline to Week 15.”

235. The February 24, 2020 Press Release expressly directs its readers to the INCREASE trial because it reports on the INCREASE trial. (Anticipated Testimony of Dr. Channick) A POSA would know the INCREASE study used Tyvaso®, the claimed dosing regimen and a pulsed inhalation device. (Anticipated Testimony of Dr. Channick.) This is because the Feb. 2020 Press Release specifically says INCREASE was a “clinical study of Tyvaso® (treprostinil) Inhalation Solution . . . .” (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063612.) The Feb. 2020 Press Release also states that the results of INCREASE were “consistent with previous Tyvaso studies in PAH and known prostacyclin-related adverse events (see the discussion of adverse events below under ‘About Tyvaso’).” (*Id.*) Further, under “About Tyvaso” in the Feb. 2020 Press Release, it states “To learn more about Tyvaso, talk with your healthcare provider. Please see Full Prescribing Information, Patient Product Information, and the TD-100 and TD-300 TYVASO® Inhalation System Instructions for Use manuals at [www.tyvaso.com](http://www.tyvaso.com) or call 1-877-UNITHER (1-877-864-8437).” (*Id.* at UTC\_LIQ00063615.)

Thus, the Press Release expressly directs POSAs to information about INCREASE and Tyvaso®, including dosing and the pulsed inhalation device. (Anticipated Testimony of Dr. Channick.)

#### **10. The INCREASE Study NEJM Publication**

236. The results of the INCREASE study were published in 2021 in the New England Journal of Medicine article titled “Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease” (“NEJM Publication”). (DTX0363, Aaron Waxman et al, *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, 384 NEW ENGLAND J. MED. 325 (2021) (UTC\_PH-ILD\_010790) (“Waxman 2021”).) Authors included Drs. Aaron Waxman, Victor Tapson, and Steven Nathan, who were the steering committee members for the INCREASE trial. (*Id.* at UTC\_PH-ILD\_010790.)

237. The NEJM publication for the INCREASE study cited to several studies including Agarwal 2015, Faria-Urbina 2018, and L. Wang, et al., noting:

Data from previously completed pilot studies suggest that inhaled treprostinil can improve hemodynamics and functional capacity in patients with group 3 pulmonary hypertension. Therefore, the objective of the INCREASE trial was to evaluate the safety and efficacy of inhaled treprostinil in patients with [PH-ILD].

(*Id.* at UTC\_PH-ILD\_010791 (citing DTX0137, Agarwal 2015, DTX0348, Faria-Urbina 2018, L. Wang, et al., *Hemodynamic and gas exchange effects of inhaled iloprost in patients with COPD and pulmonary hypertension*, Int’l J. COPD, 12:3353-60 (2017) (UTC\_PH-ILD\_010782), and DTX0346, A. Bajwa, et al., *The safety and tolerability of inhaled treprostinil in patients with pulmonary hypertension and chronic obstructive pulmonary disease*, Pulmonary Circulation, 7:82-88 (2017) (UTC\_PH-ILD\_009846)).)

238. According to Dr. Smith and Dr. Waxman, the INCREASE study results, published in the NEJM, confirmed the results seen in earlier studies that treprostinil administered to patients with PH-ILD “improved exercise capacity from baseline, assessed with the use of a 6-minute walk

test.” (DTX0363, NEJM Publication at UTC\_PH-ILD\_010790 (Abstract); Smith Depo. Tr. at 223:2-10; Waxman Depo. Tr. at 224:17-224:22, 230:1-6.) Amongst other measures, patients also showed a significant reduction in acute exacerbations and percent predicted FVC, but not absolute FVC for the intent-to-treat population. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010796 (Discussion), UTC\_PH-ILD\_010798; Nathan PI Decl., ¶ 91.) Dr. Nathan confirmed that the study demonstrated significant improvements in FVC percent predicted but not in absolute FVC (mL), and even then, only a subset of all the patients in the INCREASE study showed an improvement in FVC percent predicted. (Anticipated Testimony of Dr. Nathan; Nathan Depo. Tr. at 204:23-205:6.) The magnitude of the FVC percent predicted improvement was 1.1%. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010825 (Table S6).) UTC is conducting a subsequent study, TETON, to examine whether patients actually show an improvement in FVC. (Anticipated Testimony of Dr. Nathan; Nathan Depo. Tr. at 117:12-118:17.)

239. The NEJM Publication also includes a supplement which contains a copy of the Original INCREASE Protocol, dated Oct. 21, 2015, the Final INCREASE Protocol, Amendment 3, dated February 15, 2017, and a Study Protocol Summary of Changes document which describes the changes in the protocols. (DTX0417, NEJM Protocol Supplement, UTC\_PH-ILD\_145360.)

## **11. Lancet Paper**

240. A post-hoc analysis of the INCREASE study published in the Lancet reported PH-ILD patients experiencing improvements in FVC, including statistically significant improvements in % predicted FVC in the Intent-to-Treat population. (See DTX0009, S. Nathan, et al., *Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study*, The Lancet Respir. Med, (2021), published online June 29, 2021 [https://doi.org/10.1016/S2213-2600\(21\)00165-X](https://doi.org/10.1016/S2213-2600(21)00165-X)

((LIQ\_PH-ILD\_00000216) (“Lancet 2021”) at LIQ\_PH-ILD\_00000217, LIQ\_PH-ILD\_00000220 (Fig. 1).)

241. As described in the Lancet Paper, the INCREASE study demonstrated that following its dosing regimen, the PH-ILD patients experienced a statistically significant improvement in FVC after 8 weeks, 12 weeks or 16 weeks of administration. (See DTX0009, Lancet 2021 at LIQ\_PH-ILD\_00000216, LIQ\_PH-ILD\_00000217.)

242. Dr. Nathan stated the following in the Lancet paper regarding these FVC results, which formed the basis of the issued claims in the ’327 patent:

In conclusion, inhaled treprostinil appears to have a salutary effect on loss of lung function in patients with ILD and associated pulmonary hypertension. This finding, although intriguing and hypothesis generating, warrants further validation in a prospective, randomised, placebo-controlled study.

(*Id.* at LIQ\_PH-ILD\_00000224.)

## **12. The 2021 Tyvaso® Label**

243. Based on the results of the INCREASE study, UTC sought FDA approval to add the PH-ILD indication to Tyvaso®. (DTX0360, 2021 Tyvaso® Label at UTC\_PH-ILD\_010744.) On April 1, 2021, the FDA approved Tyvaso® for the following indication: “Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (DTX0360, 2021 Tyvaso® Label at UTC\_PH-ILD\_010744 (Indications and Usage).) The 2021 Tyvaso® label includes Section 2 on Dosing. (*Id.* at UTC\_PH-ILD\_010745-746 (Dosage and Administration).) The initial dose “should begin with 3 breaths of Tyvaso (18 mcg of treprostinil), per treatment session, 4 times daily.” (*Id.*) The maintenance dose “should be increased by an additional 3 breaths per treatment session, 4 times daily at approximately 1- to 2-week intervals.” (*Id.*) The label continues: “Studies establishing effectiveness in patients with PAH and PH-ILD have used target doses of 9 to 12 breaths per treatment sessions, 4 times daily.

If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.” (*Id.*)

244. Thus, the initial and maintenance dosing listed on the 2021 Tyvaso® label are the same for both the Group 1 PAH and Group 3 PH-ILD indications. (DTX0360, 2021 Tyvaso® Label (UTC\_PH-ILD\_010744) at UTC\_PH-ILD\_010745.) This dosing scheme matches the 2009 Tyvaso® label, which also starts with 3 breaths (18 mcg) per treatment session, 4 times daily, and allows for dose increases by 3 breaths until reaching a target dose of 9 breaths (54 mcg) per session, 4 times daily, with a maximum recommended dosage of 9 breaths per session, 4 times daily. (Anticipated testimony of Dr. Channick; DTX0357, 2009 Tyvaso® Label (UTC\_PH-ILD\_010692) at UTC\_PH-ILD\_010693.)

## **VI. NON-INFRINGEMENT**

245. As outlined here and explained in more detail in the following sections, the use of YUTREPIA does not and will not infringe the Asserted Claims of the ’327 patent.

### **A. Liquidia Does Not and Will Not Induce Infringement of Claim 1 of the ’327 Patent**

246. Liquidia does not have the intent to induce another’s direct infringement, because Liquidia’s proposed label for YUTREPIA to include the PH-ILD indication simply reflects activities already present in the public domain. (Anticipated Testimony of Dr. Channick.) As discussed in § V.B., the YUTREPIA label, with respect to the PH-ILD indication, as well as the accompanying dosing, is directed to what healthcare providers had already been doing with respect to treating PH-ILD patients and was already in the public domain. (Anticipated Testimony of Dr. Channick.) Specifically, soon after approval of Tyvaso® for treatment of PAH, healthcare providers began prescribing Tyvaso® off-label using the approved PAH dosing regimen to improve exercise capacity in their PH-ILD patients. As such, Liquidia’s proposed label for



YUTREPIA does not evidence a specific intent to induce patent infringement by another. (Anticipated Testimony of Dr. Channick.)

247. As Dr. Nathan has acknowledged, the YUTREPIA label includes the following indication: “Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126020-022.) The method of treatment described by this indication and associated dosing of inhaled treprostinil from the YUTREPIA label was already publicly disclosed and was in the public domain, such as in the 2018 article by Dr. Mariana Faria-Urbina published in the journal *Lung*, Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease (“Faria- Urbina 2018”) before the filing of the ’327 patent. (Anticipated Testimony of Dr. Channick.) Faria-Urbina 2018 is an article reflecting the work directed by Dr. Aaron Waxman at Brigham and Women’s Hospital, and according to Dr. Waxman, reflects “real-world” use of Tyvaso® to treat PH-ILD patients since 2009. (Waxman Depo. Tr. at 93:15-95:16, 229:23-230:8.) Faria-Urbina 2018 discloses using inhaled treprostinil to improve the exercise capacity of PH-ILD patients. (DTX0348, Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at UTC\_PH-ILD\_009938-939.) Specifically, in Faria-Urbina 2018, the “study population was constituted by 22 Group 3 PH patients[,]” which included nine PH-ILD patients. (*Id.*; *see also* Waxman Depo. Tr. at 95:17-96:4, 100:17-101:9.) The authors of the study reported a statistically “significant improvement in . . . 6-min walk distance (n=11, 243±106 vs. 308±109; p=0.022)” and concluded that, for “patients with Group 3 PH treated with [inhaled treprostinil,] . . . therapy with [inhaled treprostinil] significantly improved WHO-FC and 6MWT distance.” (DTX0348, Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at UTC\_PH-ILD\_009936-939; Waxman Depo. Tr. at 102:17-23.) This demonstrates that the indication in YUTREPIA’s label directed to improving exercise ability in

PH-ILD Group 3 patients was already practiced in the real world by healthcare providers and thus in the public domain. (Anticipated Testimony of Dr. Channick.)

248. The YUTREPIA label also discloses dosing for PH-ILD in accordance with that used in Faria-Urbina 2018. The recommended dosing of YUTREPIA for treprostinil-naïve patients for the PH-ILD indication is:

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Usual Dosage In Adults

YUTREPIA capsules are for oral inhalation only and should be used only with the supplied inhaler.

*YUTREPIA Dosing in treprostinil-naïve patients:*

In patients naïve to treprostinil, therapy should begin with 26.5 mcg 3 to 5 times per day, in 2 breaths based on patient response.

(DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126021.)

Similarly, the dosing of YUTREPIA for patients transitioning from Tyvaso® is:

*Dosing in patients transitioning from treprostinil inhalation solution (Tyvaso):*

Patients transitioning from treprostinil inhalation solution (Tyvaso), can begin YUTREPIA therapy 3 to 5 times per day, in 2 breaths, using the doses specified below (Table 1):

**Table 1: YUTREPIA Dosing in Patients Transitioning from Treprostinil Inhalation Solution**

Current Tyvaso Dose*	YUTREPIA Dose
Breaths	mcg
≤5	26.5
≥6 and ≤8	53
≥9 and ≤11	79.5
≥12 and ≤14	106
≥15 and ≤17	132.5
≥18	159

\*Each breath of Tyvaso delivers approximately 6 mcg of treprostinil

In treprostinil-naïve patients and those transitioning from treprostinil inhalation solution, dose increases of 26.5 mcg per dose each week may be implemented, as tolerated. The target maintenance dosage is 79.5-106 mcg, 4 times daily. Doses above 848 mcg per day have not been studied in patients with PAH.

(*Id.* at LIQ\_PH-ILD\_00126021-022.)

249. Faria-Urbina 2018 discloses Group 3 PH patients receiving inhaled treprostinil, beginning at “three breaths (18 µg) four times daily (72 µg/day)” and “increased as tolerated by three additional breaths (18 µg) per dosing session every 3-7 days to achieve a dose of at least 9-12 breaths or more (≥54 µg) four times daily (≥216 µg/day)[.]” (DTX0348, Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at UTC\_PH-ILD\_009937; *see also* Waxman Depo. Tr. at 97:7-99:15.) Thus, Faria-Urbina 2018 discloses treprostinil dosing starting at 72 µg/day (three breaths four times daily) and increasing up to at least between 216 µg/day (nine breaths four times daily) and 288 µg/day (12 breaths four times daily) or more. Similarly, for the same indication and patient population, the YUTREPIA label recommends treprostinil dosing starting at 79.5 µg/day (“26.5 mcg 3 to 5 times per day”) and increasing up to a target maintenance dose of between 318 µg/day to 424 µg/day (“79.5-106 mcg, 4 times daily”). (DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126021-022.) This demonstrates that the recommended dosing in the YUTREPIA label for PH-ILD Group 3 patients was already used in the real world by practicing healthcare providers, outside the context of a prospective clinical trial, and thus was in the public domain. (*See* Waxman Depo. Tr. at 93:15-95:16, 229:23-230:8.)

250. The deposition testimony of Dr. Rajeev Saggar, Liquidia’s Chief Medical Officer since July 2022, corroborates that Liquidia knew that treating PH-ILD patients with inhaled treprostinil to improve their exercise capacity was in the public domain. Dr. Rajeev Saggar testified that Faria-Urbina 2018 “represents patients that have used Tyvaso to treat patients with PH-ILD” and that these publications constitute “a body of evidence that’s existed in the literature for ... around 10 years ... using Tyvaso to treat PH-ILD.” (Rajeev Saggar Depo. Tr. at 207:10-208:14.)

251. Even the current Tyvaso® label uses the same dosing as Faria-Urbina 2018 in PH-ILD patients to improve their exercise capacity. (DTX0360, 2021 Tyvaso® Label (UTC\_PH-ILD\_010744) at UTC\_PH-ILD\_010744-745.) Dr. Waxman, as head of the INCREASE study steering committee, confirmed that he and the steering committee used the dosing disclosed in Faria-Urbina 2018, which was the same dosing as on the 2009 Tyvaso® label, to conduct the INCREASE study. (*Compare* DTX0348, Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at UTC\_PH-ILD\_009937, *with* DTX0360, 2021 Tyvaso® Label (UTC\_PH-ILD\_010744) at UTC\_PH-ILD\_010744-745; Waxman Depo. Tr. at 200:11-202:10, 207:14-210:5.) Dr. Waxman also confirmed that the Faria-Urbina 2018 article included essentially the same patient population as the INCREASE study. (Waxman Depo. Tr. at 224:12-25.) UTC used the same dosing regimen on its 2009 Tyvaso® label in its 2021 Tyvaso® label for the PH-ILD indication. (*Compare* DTX0357, 2009 Tyvaso® Label (UTC\_PH-ILD\_010692) at UTC\_PH-ILD\_010694, *with* DTX0073, 2021 Tyvaso® Label (LIQ\_PH-ILD\_00085434) at LIQ\_PH-ILD\_00085434.) Dr. Waxman testified that “the results you see with the original Tyvaso dosing you can get in PH-ILD with the same dosing[.]” (Waxman Depo. Tr. at 207:14-211:24.)

252. UTC and Dr. Nathan have taken the position that the indication and recommended dosing in the YUTREPIA label is evidence of Liquidia’s intent to induce direct infringement of claim 1 of the ’327 patent by healthcare providers and/or patients. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan further asserts that to directly infringe claim 1, all a healthcare provider needs to do is write a prescription for Yutrepia with the “intent and expectation” of achieving an improvement in exercise capacity, even if the patient does not experience such an improvement. (Anticipated Testimony of Dr. Nathan and Thisted.) Intent and expectation, however, are insufficient to provide direct infringement and instead, the claimed result needs to actually be

achieved. Moreover, that same indication and dosing is nothing more than what healthcare providers were practicing since at least 2009, and as such, Liquidia's YUTREPIA label merely practices what was already in the public domain with respect to the dosing of inhaled treprostinil for the improvement of exercise capacity in PH-ILD patients. (Anticipated Testimony of Dr. Channick.) Accordingly, Liquidia cannot have the specific intent to induce infringement of claim 1.

253. Moreover, to the extent that UTC claims the YUTREPIA label induces infringement, that argument supports the invalidity of the '327 patent based on the prior art. (Anticipated Testimony of Dr. Channick.) Dr. Nathan has argued that the YUTREPIA label induces healthcare providers to directly infringe the '327 patent because the YUTREPIA label is based on the INCREASE study and Liquidia has allegedly marketed and promoted YUTREPIA in the same population of PH-ILD patients that currently use UTC's Tyvaso® and Tyvaso DPI® products. (Anticipated Testimony of Dr. Nathan.) However, the methods and results of the INCREASE study have already been disclosed in the prior art, and the same prior art studies have treated the same PH-ILD population that currently is treated by Tyvaso® and Tyvaso DPI®. (Anticipated Testimony of Dr. Channick.) To the extent that UTC argues that the '327 patent is infringed by the YUTREPIA label, that interpretation supports the invalidity of the '327 patent as anticipated or obviated by the prior art references discussed herein, which applied the claimed dosing regimen to treatment of PH-ILD patients. (*See e.g.* Nathan Depo. Tr. at 214:4-17; 227:21-229:9; 230:10-19; 268:2-21.)

254. All the remaining Asserted Claims directly or indirectly depend on independent claim 1 of the '327 patent. Because Liquidia does not have the specific intent to induce

infringement of claim 1, Liquidia cannot, and does not, have the specific intent to induce infringement of the dependent Asserted Claims 2-11 and 14-19 of the '327 patent.

**B. Healthcare Providers and Patients Do Not Directly Infringe Asserted Dependent Claims 2-10 and 17-19**

255. There is no direct infringement of dependent claims 2-10 and 17-19 because there is no evidence that healthcare providers and/or patients will measure or assess any of the statistical or clinical outcomes expressly required by these claims. (Anticipated Testimony of Dr. Channick.) Asserted dependent claims 2-10 and 17-19 require the following outcome measures:

<b>Claim 2</b>	
2	The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 3</b>	
3	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 4</b>	
4	The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 5</b>	
5	The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 6</b>	
6	The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.
<b>Claim 7</b>	

7	The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.
<b>Claim 8</b>	
8	The method of claim 7, wherein the clinical worsening events comprise at least one hospitalization for cardio-pulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared to a baseline 6-minute walk distance prior to administering.
<b>Claim 9</b>	
9	The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.
<b>Claim 10</b>	
10	The method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
<b>Claim 17</b>	
17	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.
<b>Claim 18</b>	
18	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.
<b>Claim 19</b>	
19	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

256. As UTC has acknowledged, a party is only liable for direct infringement of a method claim if it practices *each step* of a patent claim in the United States. Here, dependent claims 2-10 and 17-19 require either a “statistically significant” result (claims 2, 4, 6, 7-8, 9-10) or a particular clinical outcome that must be measured (claims 3, 5, 8, 10, 17-19). (Anticipated Testimony of Dr. Channick.) There is no evidence that a healthcare provider or patient will

measure any of these statistical or clinical outcomes based on the proposed YUTREPIA label, or look to any of the non-label sources Dr. Nathan has cited as evidence of alleged inducement. Dr. Nathan has contended that the INCREASE study is included as the basis for approval of YUTREPIA in PH-ILD. (Anticipated Testimony of Dr. Nathan.) However, it is important to note that the indication language in the YUTREPIA label does not include many of the limitations of the dependent claims. (Anticipated Testimony of Dr. Channick.) The approved indication on the YUTREPIA label does not include any language pertaining to statistical significance or specific time intervals for taking measurements. (Anticipated Testimony of Dr. Channick.) It further does not mention the plasma concentration of NT-proBNP, exacerbations of ILD, clinical worsening events or forced vital capacity. (Anticipated Testimony of Dr. Channick.) Specifically, the YUTREPIA label does not direct, instruct, or teach a healthcare provider to perform the claimed test, let alone measure them and determine whether the patient achieved a statistically significant improvement (or reduction) in the outcome. Dr. Nathan is aware of these deficiencies and to overcome them, asserts that to infringe any of the dependent claims, a healthcare provider only needs to write a prescription for Yutrepia with the “intent and expectation” of achieving the claimed result. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan also opined that a healthcare provider does not need to actually measure and of the identified intended results of the dependent claims, nor do those results actually have to be achieved in order to directly infringe. (Anticipated Testimony of Dr. Nathan and Thisted.) Having an intent or expectation is insufficient to establish direct infringement of these dependent claims. The intended results of these claims need to actually be achieved.

257. Dr. Nathan has argued that peer-reviewed publications discussing the results of the INCREASE study as well as other publicly available publications, abstracts, posters, or



presentations discussing the results of the INCREASE study are evidence of infringement. (Anticipated Testimony of Dr. Nathan; Anticipated Testimony of Dr. Channick.) However, none of these materials involves the testing of YUTREPIA in any patient or study subject. In fact, these materials are limited to the use of Tyvaso® in clinical study subjects as part of the INCREASE study with defined inclusion and exclusion criteria for the patient population. (Anticipated Testimony of Dr. Channick.) Further, there is nothing in the Yutrepia label directing any healthcare provider or patient to these publications or presentations.

258. The evidence cited by Dr. Nathan and UTC is also not sufficient to prove that any future use of YUTREPIA will meet all the limitations of the dependent Asserted Claims because YUTREPIA is not a generic form of Tyvaso®. For example, YUTREPIA's formulation and mode of delivery are different than Tyvaso®. (Anticipated Testimony of Dr. Channick.) Moreover, while certain aspects of the INCREASE study are discussed in the YUTREPIA label, nearly all of the limitations in the dependent Asserted Claims appear nowhere in the INCREASE study description in the YUTREPIA label. Dr. Nathan has argued that the YUTREPIA label's limited description of certain aspects of the INCREASE study would lead a POSA to understand that the results of the INCREASE study are incorporated into the YUTREPIA label. (Anticipated Testimony of Dr. Nathan.) This is not so because there is not statement of incorporation by reference, nor is the publication or citation for the INCREASE study provided in the Yutrepia label.

**1. Claims 2, 4, 6, and 7-10 are not directly infringed because there is no evidence that any healthcare provider or patient will perform statistical analysis**

259. Claims 2, 4, 6, and 7-10 require “statistically significant” results.

260. As Dr. Nathan has acknowledged, a statistically significant result is one that is unlikely to have occurred by chance alone. To determine if the result of a particular intervention

is statistically significant, a person must select a parameter to measure, apply the intervention to a sufficiently large group to detect a meaningful difference, measure the selected parameter in each group member, aggregate the collected data, and perform statistical analysis on the data. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Dr. Ogenstad.) This Court agreed that finding “statistical significance requires data from multiple patients.” (D.I. at 149 at 6 (Memorandum Opinion on Claim Construction).) Part of conducting a statistical significance analysis includes calculating a p-value, which indicates the probability of obtaining the observed results by chance. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Dr. Ogenstad.) A low p-value, generally one less than 0.05, suggests that the results are unlikely to have happened by random chance and are more likely due to the intervention taken. (Deng Depo. Tr. at 123:10-16.)

261. Claims 2, 4, 6, and 7-10 all require a “statistically significant” change in the following clinical parameters: increase in 6MWD (claim 2), a reduction in NT-proBNP plasma concentration (claim 4), exacerbations (claim 6), clinical worsening events (claims 7 and 8), and an improvement in FVC (claims 9-10). A POSA would understand, as acknowledged by Dr. Nathan and Chunqin Deng, statistical significance cannot be determined based on results from a single patient. (Nathan Depo. Tr. at 71:9-72:3; see also Deng Depo. Tr. at 162:25-164:1.) A POSA would further understand that in order to have a statistically significant change, these claims necessitate that a healthcare provider prescribe inhaled treprostinil (apply the intervention), to multiple patients (a group large enough to detect a meaningful difference), measure one of the selected parameters in each group member, aggregate the results from the patients, and then perform statistical analysis on those results. (Anticipated Testimony of Dr. Channick; *see also* Nathan Depo. Tr. at 71:9-72:3; Deng Depo. Tr. at 162:25-164:1.) Thus, a healthcare provider will

not know or understand if they directly infringe any of claims 2, 4, 6, 7-8 and 9-10 without conducting a statistical analysis of the patients they treat. (Anticipated Testimony of Dr. Channick.)

262. UTC has not identified evidence that healthcare providers will measure statistical significance in any of the above-mentioned clinical parameters when treating patients with YUTREPIA (or any inhaled treprostinil product) outside of the context of a clinical trial. (Anticipated Testimony of Dr. Channick.) Dr. Nathan has argued that a POSA would understand that administration of YUTREPIA to at least some PH-ILD patients would result in a similar statistically significant improvement in 6MWD as demonstrated in the YUTREPIA label and the INCREASE study. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan makes an identical argument concerning the statistical significance of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the interstitial lung disease, and FVC. (Anticipated Testimony of Dr. Nathan.) However, administration of YUTREPIA, without more, is not sufficient to demonstrate direct infringement of claims 2, 4, 6, and 7-10. (Anticipated Testimony of Dr. Channick.) Instead, direct infringement of these claims requires a healthcare provider or patient to *actively measure* whether YUTREPIA administration produces the claimed statistically significant outcomes. (Anticipated Testimony of Dr. Channick.) Dr. Nathan contends that a healthcare provider does not need to measure any of the outcomes in claims 2, 4, 6, and 7-10 and does not need to aggregate the data or calculate a statistical result. According to Dr. Nathan, all that is required is for a healthcare provider to write a prescription with the intent and expectation that the claimed outcome will occur. Intent and expectation is insufficient to establish direct infringement because direct infringement requires proof that the claim outcome is actually achieved using the accused product. Dr. Thisted opines that the statistical significance requirement

of these claims is met, because INCREASE shows a statistical significance on the “population level.” But doctors do not treat patients on a population level, but instead treats each individual patient. Thus, evidence of statistical significance on a population level does not prove that a healthcare provider directly infringes these claims when treating individual patients, as healthcare providers do. Moreover, Dr. Nathan’s opinion rests on healthcare providers going outside the YUTREPIA label and reading the New England Journal of Medicine publication or the INCREASE study or other materials. (Anticipated Testimony of Dr. Channick.) There is no reference to these publications and papers in the YUTREPIA label nor is there any instruction or suggestion in the YUTREPIA label to go find these materials and review them. (Anticipated Testimony of Dr. Channick.)

263. Additionally, clinicians would not calculate statistical significance. (Anticipated Testimony of Dr. Channick.) The proposed YUTREPIA label states that this drug is indicated (in part) to improve exercise capacity in PH-ILD patients. (DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126020.) When endeavoring to improve a patient’s exercise capacity, a healthcare provider’s usual practice would be to administer YUTREPIA to one patient and monitor any improvements over time. (Anticipated Testimony of Dr. Channick.) This would not involve gathering data from multiple patients and running statistical analyses, as required by claims 2, 4, 6, and 7-10. (Anticipated Testimony of Dr. Channick.) Thus, healthcare providers prescribing YUTREPIA and patients taking YUTREPIA will not directly infringe claims 2, 4, 6, and 7-10.

**2. Claims 2, 3, 8, and 17-19 are not directly infringed because there is no evidence that healthcare providers or patients will perform or measure 6MWD**

264. Dr. Nathan has argued that use of YUTREPIA according to its label will directly infringe claims 2, 3, 8, or 17-19. (Anticipated Testimony of Dr. Nathan.) However, these claims

require doctors and patients to do more than just administer inhaled treprostinil according to the dosing covered in claim 1. (Anticipated Testimony of Dr. Channick.) They, instead, require a healthcare provider or patient to administer inhaled treprostinil over a period of at least 8 weeks, measure the 6MWD prior to administering the drug and after a period of at least 8 weeks, after 12 weeks, or after 16 weeks and, for claims 2 and 8, assess whether there is any statistically significant improvement in 6MWD. (Anticipated Testimony of Dr. Channick.)

265. There is nothing in the YUTREPIA label that instructs the measurement of 6MWD and certainly not at any of the 8, 12, or 16 week time intervals identified in claims 2, 3, 8, and 17-19. (See DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017); Anticipated Testimony of Dr. Channick.) Further, the portions of the proposed YUTREPIA label that Dr. Nathan has cited do not instruct healthcare providers or patients to perform a 6MWT. (Anticipated Testimony of Dr. Channick.) The Hodges-Lehmann estimate that Dr. Nathan has cited, for instance, only describes a statistically significant improvement in 6MWD shown in a *prior* clinical study (the INCREASE study, which was completed in 2021), using a *different* drug formulation (Tyvaso® (i.e., treprostinil inhalation solution)—not YUTREPIA (i.e., treprostinil inhalation dry powder)). (Anticipated Testimony of Dr. Channick.) The same is true of the “Forest Plot” Dr. Nathan cited, which (as Dr. Nathan described) “compares patients taking Tyvaso (treprostinil) with patients administered placebo” and shows statistically significant improvement in 6MWD. (DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126032.) Dr. Thisted will testify that none of the Asserted Claims, however, require an improvement compared to placebo. Further, a POSA reading the Hodges-Lehmann estimate and Forest Plot would only understand that a statistically significant improvement in 6MWD resulted from administration of treprostinil inhalation solution in the group of patients treated in the INCREASE study. (Anticipated

Testimony of Dr. Channick.) A POSA would not interpret this as an affirmative future instruction to measure 6MWD after weeks 8, 12 or 16, let alone treat multiple patients, measure 6MWD, aggregate the data, and perform a statistical analysis as required by the claims. (Anticipated Testimony of Dr. Channick.) UTC and Dr. Nathan have not shown that healthcare providers and/or patients will directly infringe claims 2, 3, 8, or 17-19 by following the proposed YUTREPIA label. (Anticipated Testimony of Dr. Channick.) Dr. Nathan contends that a healthcare provider does not need to measure any of the outcomes in claims 2, 3, 8, or 17-19. According to Dr. Nathan, all that is required is for a healthcare provider to write a prescription with the intent and expectation that the claimed outcome will occur. Intent and expectation is insufficient to establish direct infringement because direct infringement requires proof that the claim outcome is actually achieved using the accused product.

266. Dr. Nathan and UTC have relied on materials outside the proposed YUTREPIA label to argue that healthcare providers and patients will directly infringe claims 2, 3, 8, and 17-19. (Anticipated Testimony of Dr. Nathan.) These materials are not relevant to the direct infringement analysis because the proposed YUTREPIA label does not refer to these documents and never instructs a healthcare provider or patient to consult them. (Anticipated Testimony of Dr. Channick.) Even if these materials were relevant, however, they still would not support a finding of direct infringement. (Anticipated Testimony of Dr. Channick.)

267. Dr. Nathan cites the NEJM publication of the INCREASE study (“INCREASE publication”) to argue that a healthcare provider would infringe claims 2, 3, 8, and 17-19. (Anticipated Testimony of Dr. Nathan.) The fact that the INCREASE publication provides 6MWD results does not prove that healthcare providers or patients, and particularly those outside the context of a clinical trial, would administer YUTREPIA to multiple patients, measure 6MWD,

aggregate the data and run a statistical analysis as required by claim 2, or measure 6MWD after weeks 8, 12 or 16 to obtain a specific increase in distance walked, because there is no requirement to do so in the YUTREPIA label. (Anticipated Testimony of Dr. Channick.)

**3. Claims 4 and 5 are not directly infringed because there is no evidence that healthcare providers or patients will measure NT-proBNP**

268. Administering YUTREPIA according to the proposed YUTREPIA label will not result in direct infringement of claims 4 and 5. (Anticipated Testimony of Dr. Channick.)

269. Claim 4 requires: “a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.” (’327 patent at Claim 4.) Separate from the statistical significance aspect of claim 4, to practice claim 4, healthcare providers or patients would need to take a baseline measurement of NT-proBNP plasma concentration, as well as another measurement at least 8 weeks post-administration, and assess whether patients experienced a statistically significant reduction in plasma concentration of NT-proBNP. (Anticipated Testimony of Dr. Channick.) Claim 5 requires a reduction in “plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering[,]” which requires healthcare providers and patients to measure NT-proBNP plasma concentration prior to administration and at least once after 8 weeks or later. (*Id.*; Anticipated Testimony of Dr. Channick.) It additionally requires a reduction of greater than 200 pg/ml. (*Id.*)

270. The proposed YUTREPIA label never mentions NT-proBNP, let alone provide any instructions to measure this parameter after weeks 8, 12 or 16 as claimed. (Anticipated Testimony of Dr. Channick.) This alone is enough to defeat any allegations of direct infringement of claims 4 and 5. (Anticipated Testimony of Dr. Channick.) For example, the YUTREPIA PH-ILD indication is not directed to any particular reduction in NT-proBNP levels. Moreover, the

discussion of the INCREASE study in the YUTREPIA label makes no mention of NT-proBNP. (See DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126031-033.) Furthermore, outside of clinical trial settings, healthcare providers treating PH-ILD patients do not routinely measure NT-proBNP levels. (Anticipated Testimony of Dr. Channick.) This alone is enough to defeat any allegations of direct infringement of claims 4 and 5. Dr. Nathan contends that a healthcare provider does not need to measure any of the outcomes in claims 4 and 5. According to Dr. Nathan, all that is required is for a healthcare provider to write a prescription with the intent and expectation that the claimed outcome will occur. Intent and expectation is insufficient to establish direct infringement because direct infringement requires proof that the claim outcome is actually achieved using the accused product.

271. The proposed YUTREPIA label does not mention the NEJM INCREASE publication that Dr. Nathan cited in support of direct infringement of claims 4 and 5, nor does the label direct a healthcare provider or patient to review this publication. Even if the Court were to consider the INCREASE publication, it is not an instruction to healthcare providers or patients to actually measure NT-proBNP before or after administration of YUTREPIA. (Anticipated Testimony of Dr. Channick.) In any event, publication is not proof of future direct infringement by healthcare providers because it merely describes past data of a different drug, which does not instruct healthcare providers and/or patients to practice the steps outlined in claims 4 and 5. (Anticipated Testimony of Dr. Channick.) The same is true of the Product Dossier (LIQ\_PH-ILD\_00146984) Dr. Nathan cited in support of direct infringement of claims 4 and 5, which again is not referenced in the YUTREPIA label. In addition, Mike Post, the Vice President of Marketing at Liquidia, indicated that the Product Dossier on which Dr. Nathan relied is only intended for



payors to educate them about YUTREPIA concerning their formularies; it is not intended to be shown to healthcare providers or patients. (Anticipated Testimony of Dr. Channick.)

272. Additionally, there is no evidence that administering YUTREPIA achieves a reduction of NT-proBNP plasma concentration by 200 pg/ml, as required by claim 5. To begin with, this specific NT-proBNP outcome is nowhere to be found in the YUTREPIA label. To meet this claim, a healthcare provider or patient would need to record baseline and follow-up measurements of NT-proBNP plasma concentration, and then actually achieve a reduction of 200 pg/ml. (Anticipated Testimony of Dr. Channick.) Dr. Nathan cited the INCREASE publication to argue that YUTREPIA administration will achieve this clinical result. Setting aside the fact that the proposed YUTREPIA label never cites this publication (and, thus, never instructs healthcare providers or patients to follow its teachings), a healthcare provider following this publication's teachings would still not directly infringe claim 5. This publication describes the effects of Tyvaso® administration on NT-proBNP levels. A POSA reading this publication would not make the leap that YUTREPIA administration would result in the same NT-proBNP levels. (Anticipated Testimony of Dr. Channick.) Put another way, UTC has pointed to no evidence—whether in the proposed YUTREPIA label or outside of it—that a patient is likely to experience a reduction of 200 pg/ml after being administered YUTREPIA. (Anticipated Testimony of Dr. Channick.) Further, because measuring NT-proBNP levels was not necessary for FDA approval of Tyvaso®, healthcare providers or patients would not understand this to be a necessary clinical parameter to monitor when administering YUTREPIA. This provides an additional reason why UTC has not shown direct infringement of claim 5.

**4. Claim 6 is not directly infringed because there is no evidence that healthcare providers or patients will measure exacerbations of interstitial lung disease**

273. Claim 6 requires a “statistically significant reduction of at least one exacerbations of the interstitial lung disease.” (’327 patent, cl. 6.) The ’327 patent describes an exacerbation of interstitial lung disease as “[a]n exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality.” (*Id.* at 22:12-15, 31:4-7.) Dr. Nathan has not provided evidence that healthcare providers and/or patients will directly infringe claim 6 or that administering YUTREPIA according to the proposed YUTREPIA label will result in direct infringement of claim 6. (Anticipated Testimony of Dr. Channick.)

274. The proposed YUTREPIA label never mentions exacerbations of the interstitial lung disease, let alone provides any instructions to measure this parameter. For instance, the PH-ILD indication on the proposed YUTREPIA label is not directed to any particular exacerbation of the interstitial lung disease. Moreover, the discussion of the INCREASE study in the proposed YUTREPIA label makes no mention of exacerbations of the interstitial lung disease. (*See* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_001260) at LIQ\_PH-ILD\_00126031-033.) This alone is enough to defeat any allegations of direct infringement of claim 6. Dr. Nathan contends that a healthcare provider does not need to measure the outcome in claim 6. According to Dr. Nathan, all that is required is for a healthcare provider to write a prescription with the intent and expectation that the claimed outcome will occur. Intent and expectation is insufficient to establish direct infringement because direct infringement requires proof that the claim outcome is actually achieved using the accused product.

275. Dr. Nathan referenced the NEJM INCREASE publication, post-hoc analyses of the INCREASE study, and the INCREASE clinical study report to argue that YUTREPIA

administration will achieve statistically significant reductions in disease exacerbations. (Anticipated Testimony of Dr. Nathan.) The YUTREPIA label does not make reference to the INCREASE publication, post-hoc analyses of the INCREASE study, or the INCREASE clinical study report, nor does the label direct healthcare providers or patients to seek these references out. The INCREASE clinical study report does not appear to be a public document that healthcare providers or patients would ever be able to access (the first page states “All content contained herein is confidential and proprietary information of United Therapeutics Corporation and shall not be disclosed in whole or in part except as permitted by a signed contract with United Therapeutics Corporation”). (DTX0374, INCREASE Clinical Study Report (UTC\_PH-ILD\_055371) at UTC\_PH-ILD\_055371.) Even if the Court were to consider these documents, it is not an instruction to healthcare providers or patients to actually measure at least one exacerbations of the interstitial lung disease before or after administration of YUTREPIA. (Anticipated Testimony of Dr. Channick.) And, because reducing exacerbations in interstitial lung disease was not necessary for FDA approval of Tyvaso®, healthcare providers or patients would not understand this to be a necessary clinical parameter to monitor when administering YUTREPIA. (Anticipated Testimony of Dr. Channick.)

**5. Claims 7 and 8 are not directly infringed because there is no evidence that healthcare providers or patients will measure clinical worsening events**

276. Administering YUTREPIA according to the proposed YUTREPIA label will not result in direct infringement of claims 7 and 8. The '327 patent describes that “clinical worsening event(s) may include one or more of hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death or a lung transplantation.” ('327 patent at 19:57-60.)

277. To practice claim 7, healthcare providers and patients would need to monitor the clinical worsening events experienced due to interstitial lung disease and determine whether YUTREPIA administration produces a statistically significant result. ('327 patent at Claim 7.) Achieving a statistically significant reduction in clinical worsening events requires measuring clinical worsening events due to ILD, aggregating data from multiple patients and performing statistical analyses, which the proposed YUTREPIA label does not instruct and which is not part of routine clinical practice. (Anticipated Testimony of Dr. Channick.) This alone is enough to defeat any allegations of direct infringement of claim 7.

278. In addition to not instructing healthcare providers and patients to perform statistical analyses, the proposed YUTREPIA label does not instruct measurement of clinical worsening events experienced due to interstitial lung disease, as required by claim 7. A physician would not be able to measure a “reduction” in clinical worsening events when treating individual patients because, unlike in a clinical trial, there is no control group with which the physician may draw a comparison. (Anticipated Testimony of Dr. Channick.) Additionally, the proposed YUTREPIA label mentions time to clinical worsening events *due to PH-ILD*, whereas claim 7 requires measuring “clinical worsening events *due to the interstitial lung disease*[,]” not PH-ILD. (Compare DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126033 (Table 3: Clinical Worsening Events (PH-ILD) and Figure 5: Kaplan-Meier Plot of Time to Clinical Worsening Events (PH-ILD)), with '327 patent at Claim 7 (emphasis added).) PH-ILD and interstitial lung disease are standalone conditions; not every patient that has interstitial lung disease will develop PH-ILD. (Anticipated Testimony of Dr. Channick.) This discrepancy in disease indication between the label and claim 7 provides yet another reason why UTC has failed to demonstrate direct infringement. Dr. Nathan contends that a healthcare provider does not need

to measure the outcome of claim 7. According to Dr. Nathan, all that is required is for a healthcare provider to write a prescription with the intent and expectation that the claimed outcome will occur. Intent and expectation is insufficient to establish direct infringement because direct infringement requires proof that the claim outcome is actually achieved using the accused product.

279. The proposed YUTREPIA label does not mention the INCREASE publication that Dr. Nathan cited, nor does it direct healthcare providers or patients to review this publication. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) In any event, the INCREASE publication is not a direction or instruction to healthcare providers or patients to measure clinical worsening events due to ILD after administration of YUTREPIA. This publication merely describes past data of a different drug, which does not instruct healthcare providers to practice the steps outlined in claim 7. The same is true of the marketing materials that Dr. Nathan cited. As discussed above, the Product Dossier Dr. Nathan cited will never be shown to healthcare providers or patients as it is intended for payors, so cannot be used to establish direct infringement. The remaining marketing materials cited by Dr. Nathan merely show previous use of Tyvaso®, which does not amount to an instruction for healthcare providers or patients to measure a reduction in clinical worsening when administering YUTREPIA. For these reasons, Dr. Nathan has not shown direct infringement of claim 7. (Anticipated Testimony of Dr. Channick.)

280. Healthcare providers and patients following the proposed YUTREPIA label will not directly infringe claim 8. Claim 8 requires the clinical worsening event to include at least one hospitalization for cardio-pulmonary indication and a decrease in 6MWD by more than 15%. Because claim 8 depends on claim 7, healthcare providers and patients must practice all the requirements of claim 7 in order to directly infringe claim 8. As discussed above, a healthcare provider or a patient would not directly infringe claim 7. Because healthcare providers and patients

will not directly infringe claim 7, they will not directly infringe claim 8. Further, Dr. Nathan contends that a healthcare provider does not need to measure the outcome of claim 8. According to Dr. Nathan, all that is required is for a healthcare provider to write a prescription with the intent and expectation that the claimed outcome will occur. Intent and expectation is insufficient to establish direct infringement because direct infringement requires proof that the claim outcome is actually achieved using the accused product.

**6. Claims 9 and 10 are not directly infringed because there is no evidence that healthcare providers or patients will measure FVC**

281. Administering YUTREPIA according to the proposed YUTREPIA label will not result in direct infringement of claims 9 and 10.

282. Claim 9 requires “a statistically significant improve[ment] of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks” of administering inhaled treprostinil. (’327 patent at Claim 9.) Claim 10 adds further requirements, covering the “method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.” (*Id.* at Claim 10.) FVC, or forced vital capacity, refers to the maximum volume of air that a patient is able to forcibly expel from their lungs. (Anticipated Testimony of Dr. Channick.) Accordingly, claim 9 requires that a doctor or patient measure FVC at baseline and again at least 8 weeks after administering inhaled treprostinil, and then achieve a statistically significant result. Claim 10 adds the requirement that the improvement in the patient must be at least 20 ml after at least 8 weeks of administering the drug.

283. Setting aside the statistical significance requirements of claims 9 and 10, to practice claim 9, a healthcare provider or patient must measure FVC at baseline and again after 8, 12 or 16 weeks after administering inhaled treprostinil. (’327 patent at Claim 9.) Claim 10 includes all the

requirements of claim 9 and adds the requirement of an improvement in FVC of at least 20 ml after 8, 12, or 16 weeks.

284. The proposed YUTREPIA label makes no mention of FVC, let alone provide an instruction or directive to a healthcare provider to measure FVC during the course of YUTREPIA treatment of PH-ILD patients after week 8, 12, or 16. Thus, there would be no direct infringement of claims 9 and 10 because there is no information regarding FVC in the YUTREPIA label or performing the step of measuring FVC. Further, a healthcare provider or patient would have no reason to expect that YUTREPIA (which is a different formulation from Tyvaso®) would produce these results. (Anticipated Testimony of Dr. Channick.) For one, FVC was not a primary endpoint in the INCREASE study, meaning that it was not required for FDA approval. If an endpoint was not required for FDA approval and the label does not mention it, a healthcare provider would not independently measure that endpoint (and, if the healthcare provider were to measure that endpoint, it would be on his own accord and not per the instruction of the label). (Anticipated Testimony of Dr. Channick.) This provides an additional reason why the proposed YUTREPIA label does not lead healthcare providers or patients to directly infringe claims 9 or 10. Dr. Nathan contends that a healthcare provider does not need to measure the outcomes in claims 9 and 10. According to Dr. Nathan, all that is required is for a healthcare provider to write a prescription with the intent and expectation that the claimed outcome will occur. Intent and expectation is insufficient to establish direct infringement because direct infringement requires proof that the claim outcome is actually achieved using the accused product.

285. The proposed YUTREPIA label also does not mention the NEJM INCREASE publication, the INCREASE study report, or the post-hoc analyses that Dr. Nathan cited, nor does the label direct a healthcare provider or patient to review these documents. Moreover, these

references do not actually instruct a healthcare provider or patient to measure FVC, let alone obtain a particular improvement of 20 ml after weeks 8, 12 or 16, and is thus not evidence of direct infringement. In any event, none of these studies would cause a healthcare provider to directly infringe claims 9 or 10. These studies merely describe past FVC measurements of a different drug, which does not instruct healthcare providers to practice the steps outlined in claims 9 or 10. (Anticipated Testimony of Dr. Channick.)

286. Additionally, data for FVC addresses lung function and is used as a safety measure, not as a measure of PH-ILD, or exercise capacity in PH-ILD patients. Therefore, healthcare providers and patients would not have a reason to monitor FVC when administering YUTREPIA according to the proposed YUTREPIA label. (Anticipated Testimony of Dr. Channick.)

287. Accordingly, administering YUTREPIA according to the proposed YUTREPIA label will not lead to direct infringement of claims 9 and 10 and the evidence cited by Dr. Nathan is insufficient to show that healthcare providers and/or patients are likely to practice all the limitations of claims 9 and 10.

**C. Liquidia Does Not Induce Infringement of Any Dependent Claim**

**1. Liquidia does not induce infringement of claims 2-10 and 17-19 because there is no evidence of direct infringement by third parties**

288. For the reasons discussed in Section VI.B above, healthcare providers and patients do not directly infringe asserted claims 2-10 and 17-19. Because there is no direct infringement of asserted claims 2-10 and 17-19 by any third party, it follows that Liquidia cannot induce infringement of those claims.



**2. Liquidia does not induce infringement of claims 2, 4, 6, and 7-10 because it does not instruct or encourage determining whether the patient achieved a statistically significant result**

289. Claims 2, 4, 6, and 7-10 of the '327 patent all require that the method of treatment of claim 1 achieve “statistically significant” improvements in six-minute walk distance, plasma concentration of NT-proBNP, exacerbations of interstitial lung disease, clinical worsening events, and FVC. To achieve an improvement in these areas and confirm its statistical significance, the person practicing the method of treatment must select a metric to measure, apply the treatment to a sufficiently large group of patients, measure the selected metric in each patient, aggregate the collected data, and perform statistical analysis on the data. (Anticipated Testimony of Dr. Channick.) The YUTREPIA label does not instruct or encourage these steps. Moreover, the YUTREPIA label says nothing with respect to statistical significance related to plasma concentration of NT-proBNP, exacerbations of interstitial lung disease, clinical worsening events, and FVC. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).)

290. UTC cannot argue that Liquidia instructs or encourages healthcare providers and/or patients to treat a sufficiently large number of patients, measure the metric of interest, aggregate the collected data, and perform statistical analysis on the data. (Anticipated Testimony of Dr. Channick.) There is nothing in the YUTREPIA label, Liquidia’s marketing materials, or any other document, showing that Liquidia will instruct or encourage healthcare providers and/or patients to treat a sufficiently large number of patients, measure the metric of interest, aggregate the collected data, and perform statistical analysis on the data. (Anticipated Testimony of Dr. Channick.)

291. UTC’s and Dr. Nathan’s position that the YUTREPIA label induces infringement is contradicted by Dr. Nathan himself. Dr. Nathan has commented that he is careful to instruct patients to use the drug as the label directs and that patients administer drugs in accordance with their doctor’s orders, and that when he instructs a patient to follow the directions on a drug’s label,

they do so. (Anticipated Testimony of Dr. Nathan.) There is nothing in the YUTREPIA label instructing healthcare providers or patients to administer YUTREPIA to a sufficiently large number of patients, measure the metric of interest, aggregate the collected data, and perform statistical analysis on the data.

292. Instead, Dr. Nathan has argued that because the clinical studies section of the YUTREPIA label relies solely on the INCREASE study and its results to support YUTREPIA's PH-ILD indication, and because the results and methods of the INCREASE study are described in the YUTREPIA label and publications, abstracts, and presentations related to the INCREASE study, the YUTREPIA label instructs, encourages, recommends and promotes the use of the methods described in the INCREASE study in order to obtain the results achieved by the INCREASE study. (Anticipated Testimony of Dr. Nathan.) Reference to the INCREASE study, however, is not an instruction to perform any testing, let alone treat patients and conduct a statistical analysis. Moreover, the YUTREPIA label describes only certain aspects of the INCREASE study, and it does not instruct healthcare providers or patients to administer YUTREPIA to a sufficiently large number of patients, measure the metric of interest, aggregate the collected data, and perform statistical analysis on the data. (DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126031-033.) In other words, contrary to what Dr. Nathan has suggested, the YUTREPIA label does not instruct, encourage, recommend, and/or promote the use of the methods described in the INCREASE study in order to obtain the results achieved by the INCREASE study. (Anticipated Testimony of Dr. Channick.)

293. Additionally, the YUTREPIA label does not instruct or encourage healthcare providers or patients to review information outside the label, as Dr. Nathan has suggested. This is particularly true when, as here, the label itself provides information sufficient for the safe and

efficacious administration of the drug. (Anticipated Testimony of Dr. Channick.) Dr. Nathan has agreed, admitting that healthcare providers would expand their review of the relevant study to include publications, abstracts, and/or presentations related to this study if they desired to obtain a more comprehensive picture of the relevant study's methods, results, and conclusions. (Anticipated Testimony of Dr. Nathan.) Thus, even if a healthcare provider or patient were to review material outside the YUTREPIA label, it would be out of their own curiosity and not based on an instruction or direction by Liquidia. (Anticipated Testimony of Dr. Channick.)

294. While the YUTREPIA label does discuss certain aspects of the INCREASE study, it does not incorporate the INCREASE study by reference nor does it cite to the INCREASE publication. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) Further, the YUTREPIA label's discussion of the INCREASE study, which is limited in an inhaled solution of treprostinil and not a dry powder formulation like YUTREPIA, makes no mention of NT-proBNP, exacerbations of ILD, or FVC, and it does not disclose a statistically significant reduction of clinical worsening events. (*See id.* at LIQ\_PH-ILD\_00126031-033.) Just because a reference was publicly available does not necessarily mean that it provides the requisite proof of intent to induce infringement. The proposed label would, instead, need to explicitly direct healthcare providers and patients to these references to rise to the level of induced infringement. Otherwise, *every* drug manufacturer would be liable for induced infringement—regardless of what their label stated—on the basis that publicly available knowledge about the branded drug exists vis-à-vis prior clinical studies. Simply knowing that a healthcare provider might refer to the INCREASE publication is not sufficient evidence of Liquidia's intent to induce infringement of the Asserted Claims.

295. A healthcare provider administering a drug like YUTREPIA would not routinely aggregate patient data nor calculate the statistical significance of the patients' improvements. (Anticipated Testimony of Dr. Channick.) Further, a statistically significant result cannot be achieved with the treatment of just one patient, and the YUTREPIA label does not instruct or encourage the treatment of multiple patients to ensure that the results are statistically significant. (See generally DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).)

296. It is irrelevant to the issue of induced infringement whether the administration of YUTREPIA will result in one or more of the statistically significant outcomes described in claims 2, 4, 6, and 7-10. (Anticipated Testimony of Dr. Channick.) The proper question is whether Liquidia specifically intends for a healthcare professional or patient to directly infringe claims 2, 4, 6, and 7-10. Mere knowledge of potential infringement is not sufficient to establish that Liquidia has induced that infringement. Because the proposed YUTREPIA label does not provide an instruction to assess statistical significance, Liquidia does not induce infringement of claims 2, 4, 6, and 7-10. (Anticipated Testimony of Dr. Channick.)

**3. Liquidia does not induce infringement of claims 2, 3, 8, and 17-19 because there is no evidence that healthcare providers or patients will perform or measure 6MWD**

297. Claims 2, 3, 8, and 17-19 of the '327 patent all require measuring increases or decreases in six-minute walk distance at certain time intervals. To practice claims 2, 3, and 17-19, a healthcare provider or patient must administer inhaled treprostinil over at least 8 weeks, 12 weeks, or 16 weeks and measure the six-minute walk distance prior to and after the administration of the drug. Claim 8 depends from Claim 7 which is directed to the statistically significant reduction of clinical worsening events due to interstitial lung disease. Claim 8 defines one of the potential clinical worsening events as "a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering." ('327 patent at Claim 8.)

Therefore, in order for a healthcare provider or patient to assess whether there has been a decrease in 6MWD, they must measure 6MWD prior to treprostinil administration and compare that value to 6MWD taken at certain time intervals (after weeks 8, 12, or 16) during treprostinil treatment. (Anticipated Testimony of Dr. Channick.) Claim 2 additionally requires assessing the statistical significance of the improvement. ('327 patent at Claim 2.) However, the YUTREPIA label does not instruct doctors or patients to perform these steps. Specifically, the YUTREPIA label does not instruct any healthcare provider or patient to perform a 6MWD test before administration and again after 8, 12, or 16 weeks. Moreover, the YUTREPIA label does not instruct or encourage that a certain distance needs to be achieved by these time points, as required by claim 3 (10 m after weeks 8, 12 or 16), claim 8 (decrease in 6MWD by at least 15% as compared to baseline), claim 17 (10 m after 8 weeks), claim 18 (15 m after 12 weeks), and claim 19 (15 m after 16 weeks).

298. While the YUTREPIA label does discuss improvements in six-minute walk distance, it only does so in the context of clinical trials with Tyvaso® (the TRIUMPH and INCREASE trials), and in any case the label does not instruct or encourage doctors or patients to *measure* six minute walk distance or that certain distances will be achieved upon administration of YUTREPIA. (See DTX0118, YUTREPIATM Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126029-033.) Further, even if a healthcare provider did measure 6MWD, that is not sufficient to show inducement by Liquidia because mere knowledge of direct infringement is insufficient to establish induced infringement. Liquidia must have the specific intent to have a healthcare provider measure 6MWD after the claimed 8, 12 or 16 week time intervals and for the reasons discussed herein, there is no evidence to support that specific intent. (Anticipated Testimony of Dr. Channick.)

299. As discussed in Section VI.C.2, the YUTREPIA label does not incorporate the INCREASE study by reference nor does it cite to the INCREASE publication, although it does discuss certain aspects of the INCREASE study. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) As discussed in Sections V.B.4 and V.C.2., Dr. Nathan's argument that physicians will administer YUTREPIA to PH-ILD patients with the intent to achieve the same results UTC observed in the INCREASE study erroneously expands the scope of the YUTREPIA label to include information that simply is not present. (Anticipated Testimony of Dr. Channick.)

300. As discussed in Section V.B.2, certain results of the INCREASE study, such as the Hodges-Lehmann estimate and the Forest Plot in the YUTREPIA label, also are not an instruction or encouragement to measure and statistically analyze six-minute walk distance data. (*See* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126031-032.) A physician administering YUTREPIA would not have the intent to achieve the same results as shown in the INCREASE study, or from any clinical study for that matter. (Anticipated Testimony of Dr. Channick.) Rather, a physician's intent in administering YUTREPIA would be to deliver the drug in a safe and efficacious manner to improve how the patient feels and functions. (Anticipated Testimony of Dr. Channick.) Also, the intent of individual physicians is not at issue in an induced infringement inquiry and Liquidia's knowledge of potential infringement is not evidence that Liquidia has the specific intent to induce that direct infringement. Thus, contrary to Dr. Nathan's Arguments and the position taken by UTC, the YUTREPIA label does not support finding Liquidia's specific intent to induce infringement of the '327 patent. (Anticipated Testimony of Dr. Channick.) Furthermore, performance and measurement of the six-minute walk distance is not routinely conducted outside the context of PH-ILD clinical trials.

301. For the reasons above, Liquidia does not induce infringement of claims 2, 3, 8, and 17-19 of the '327 patent.

**4. Liquidia does not induce infringement of claims 4 and 5 because it does not instruct or encourage measurement of NT-proBNP**

302. Claim 4 of the '327 patent requires a “statistically significant reduction of a plasma concentration of NT-proBNP” and claim 5 requires a reduction in “plasma concentration of NT-proBNP in the patient by at least 200 pg/ml[.]” ('327 patent at Claims 4, 5.) Both claims 4 and 5 require taking a baseline measurement of plasma concentration of NT-proBNP, taking another measurement after administering YUTREPIA, and determining the reduction in plasma concentration of NT-proBNP. However, the YUTREPIA label does not even mention NT-proBNP, much less instruct healthcare providers or patients to measure plasma NT-proBNP levels. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) This is consistent with the YUTREPIA label’s approved indications which also do not mention NT-proBNP at all—“Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability” and “Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (*Id.* at LIQ\_PH-ILD\_00126020.) Additionally, a healthcare provider administering a drug like YUTREPIA would not routinely measure plasma NT-proBNP levels. (Anticipated Testimony of Dr. Channick.)

303. To the extent healthcare providers do measure NT-proBNP and obtain the claimed outcome measure in claims 4 and 5, this is also insufficient to establish that Liquidia induces infringement of these claims. As discussed above, mere knowledge that a healthcare provider directly infringes is insufficient for induced infringement because Liquidia must have the specific intent to cause that direct infringement. As discussed herein, there is simply no mention of NT-proBNP in the YUTREPIA label, no instruction or direction to measure NT-proBNP, or to obtain

a specific result, as required by claim 5 (reduction of 200 pg/ml after weeks 8, 12 or 16). Thus, Liquidia does not direct or instruct the performance of these steps, and therefore, does not induce infringement of these claims. (Anticipated Testimony of Dr. Channick.)

304. Dr. Nathan has attempted to expand the scope of the YUTREPIA label to encompass NT-proBNP-related results that are disclosed only in the INCREASE publication but not in the YUTREPIA label by arguing that based on the contents of the YUTREPIA label and related INCREASE clinical data, physicians will administer YUTREPIA to PH-ILD patients with the intent to achieve the same results UTC observed in the INCREASE study. (Anticipated Testimony of Dr. Nathan.) More specifically, Dr. Nathan has argued that physicians would administer YUTREPIA to PH-ILD patients with the intended purpose and expectation that at least some of these PH-ILD patients would achieve reductions of plasma concentration of NT-proBNP. (Anticipated Testimony of Dr. Nathan.) However, a physician administering YUTREPIA would not have the intent to achieve the same results as shown in the INCREASE study, or from any clinical study for that matter. (Anticipated Testimony of Dr. Channick.) Rather, a physician's intent in administering YUTREPIA would be to deliver the drug in a safe and efficacious manner to improve how the patient feels and functions. Dr. Nathan's opinion about a *physician's* "intent" does not establish induced infringement by *Liquidia*. Moreover, a healthcare provider or patient would not need to review materials not provided by or cited to by the label, especially when the label itself provides information sufficient for the safe and efficacious administration of the drug. (Anticipated Testimony of Dr. Channick.) Because the YUTREPIA label already includes instructions sufficient for the safe and efficacious administration of YUTREPIA and does not include any instruction directing doctors and patients to the INCREASE publication, physicians administering YUTREPIA would not review the INCREASE publication and would not have the



intended purpose and expectation to reduce plasma concentration of NT-proBNP. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) Even if a healthcare provider or patient were to review material outside the YUTREPIA label, it would be of their own volition and not based on an instruction or direction by Liquidia. (Anticipated Testimony of Dr. Channick.)

305. For the reasons discussed above, Liquidia does not induce infringement of claims 4 and 5 of the '327 patent. (Anticipated Testimony of Dr. Channick.)

**5. Liquidia does not induce infringement of claim 6 because it does not instruct or encourage measuring exacerbation of the interstitial lung disease**

306. Claim 6 of the '327 patent requires a “statistically significant reduction of at least one exacerbations of the interstitial lung disease,” and thus requires, similar to claims 4 and 5, monitoring baseline exacerbations of interstitial lung disease, quantifying the exacerbations again after administration of YUTREPIA, and then conducting a statistical analysis of the reductions of at least one exacerbation.

307. The YUTREPIA label does not include any indication, instruction, or even any mention of exacerbations of interstitial lung disease. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) Furthermore, healthcare providers prescribing drugs like YUTREPIA, do not routinely monitor for exacerbations specific to interstitial lung disease in PH-ILD patients. (Anticipated Testimony of Dr. Channick.) In fact, a healthcare provider cannot assess whether there is a “reduction” in exacerbations from any source when treating individual PH-ILD patients in the hospital because, unlike in a clinical trial, there is no control group from which they can draw a comparison, and they do not know the number of exacerbations an individual specific patient would have achieved in the absence of treprostinil treatment. (Anticipated Testimony of Dr. Channick.)

308. Dr. Nathan has improperly expanded the alleged scope of the YUTREPIA label to cover exacerbations of the interstitial lung disease, results that are disclosed only in the INCREASE publication, despite the YUTREPIA label not even mentioning “exacerbations of the interstitial lung disease.” Dr. Nathan has argued that based on the contents of the YUTREPIA label and related INCREASE clinical data, physicians will administer YUTREPIA to PH-ILD patients with the intent to achieve the same results UTC observed in the INCREASE study. (Anticipated Testimony of Dr. Nathan.) More specifically, Dr. Nathan has argued that physicians would administer YUTREPIA to PH-ILD patients with the intended purpose and expectation that at least some of these PH-ILD patients would achieve reductions in exacerbations of [interstitial lung] disease. (Anticipated Testimony of Dr. Nathan.) However, a physician administering YUTREPIA would not have the intent to achieve the same results as shown in the INCREASE study, or from any clinical study for that matter. (Anticipated Testimony of Dr. Channick.) Rather, a physician’s intent in administering YUTREPIA would be to deliver the drug in a safe and efficacious manner to improve how the patient feels and functions. (Anticipated Testimony of Dr. Channick.) Dr. Nathan’s opinion regarding a physician’s “intent” is not evidence of Liquidia inducing infringement, as mere knowledge of possible infringement is insufficient to establish induced infringement. Further, a healthcare provider or patient would not review materials not cited by the label, especially when, as here, the label itself provides information sufficient for the safe and efficacious administration of the drug. (Anticipated Testimony of Dr. Channick.) The YUTREPIA label already includes instructions sufficient for the safe and efficacious administration of YUTREPIA and does not include any instruction directing doctors and patients to the INCREASE publication. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) Thus, healthcare providers administering YUTREPIA would not review the

INCREASE publication and would not intend or expect to reduce exacerbations specific to interstitial lung disease. (Anticipated Testimony of Dr. Channick.) Even if a healthcare provider or patient were to review material outside the YUTREPIA label, it would be of their own volition and not based on an instruction or direction by Liquidia. (Anticipated Testimony of Dr. Channick.)

309. For the reasons discussed herein, Liquidia does not induce infringement of claim 6 of the '327 patent.

**6. Liquidia does not induce infringement of claims 7 and 8 because the YUTREPIA label does not mention or describe clinical worsening events due to interstitial lung disease or a reduction in clinical worsening events**

310. Claim 7, from which claim 8 depends, requires that the clinical worsening be “due to the *interstitial lung disease*.” ('327 patent at Claim 7.) However, the YUTREPIA label only discusses clinical worsening events as related to a cardiopulmonary indication or arising from PH-ILD generally, rather than ILD specifically. (DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017) at LIQ\_PH-ILD\_00126032.) Additionally, the YUTREPIA label, in describing results from the INCREASE study, states that “treatment with treprostinil inhalation solution demonstrated a statistically significant increase in the time to first clinical worsening event ... and a 39% overall reduction in the risk of a clinical worsening event[.]” *Id.* at LIQ\_PH-ILD\_00126032-033.) Given that healthcare providers, including Dr. Nathan, testified that treatment with inhaled treprostinil treats the pulmonary hypertension component, but not the ILD component, of PH-ILD, this result described in the YUTREPIA label also arises from PH-ILD, and not from ILD. (Anticipated Testimony of Dr. Channick.)

311. PH-ILD and ILD are distinct diseases and many ILD patients never develop PH-ILD. (Anticipated Testimony of Dr. Channick.) Claim 7 clearly requires that the clinical worsening stem from the ILD, and not from PH-ILD. (Anticipated Testimony of Dr. Channick.)

Because the YUTREPIA label only describes clinical worsening that arises from PH-ILD but not from ILD, the YUTREPIA label cannot instruct or encourage monitoring for clinical worsening events due to ILD. (Anticipated Testimony of Dr. Channick.)

312. The YUTREPIA label does not include any express indication or instruction regarding the monitoring of exacerbations of interstitial lung disease. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) Furthermore, doctors cannot assess whether there is a reduction in clinical worsening events in their everyday clinical practice—doctors would have no control group to they could draw a comparison. (Anticipated Testimony of Dr. Channick.)

313. Dr. Nathan’s arguments to expand the scope of the YUTREPIA label are unavailing. Dr. Nathan has argued that based on the contents of the YUTREPIA label and related INCREASE clinical data, physicians will administer YUTREPIA to PH-ILD patients with the intent to achieve the same results UTC observed in the INCREASE study. (Anticipated Testimony of Dr. Nathan.) More specifically, Dr. Nathan has argued that physicians would administer YUTREPIA to PH-ILD patients with the intended purpose and expectation that at least some of these PH-ILD patients would achieve reductions of clinically worsening events. (Anticipated Testimony of Dr. Nathan.) However, a physician administering YUTREPIA would not have the intent to achieve the same results as shown in the INCREASE study, or from any clinical study for that matter. (Anticipated Testimony of Dr. Channick.) Rather, a physician’s intent in administering YUTREPIA would be to deliver the drug in a safe and efficacious manner to improve how the patient feels and functions. (Anticipated Testimony of Dr. Channick.) Dr. Nathan’s opinions regarding the “intent” of a physician are not evidence of Liquidia’s specific intent to induce infringement. A healthcare provider or patient would not review materials extraneous to the label, especially when the label itself provides sufficient instructions for the safe

and efficacious administration of the drug, which the YUTREPIA label already includes. (Anticipated Testimony of Dr. Channick.) Because the YUTREPIA label does not include any instruction directing doctors and patients to the INCREASE publication, doctors administering YUTREPIA would not review the INCREASE publication and would not intend or expect to reduce clinical worsening events due to interstitial lung disease. (Anticipated Testimony of Dr. Channick.) Even if a doctor were to review material outside the YUTREPIA label, it would be of their own volition and not based on an instruction or direction from Liquidia. (Anticipated Testimony of Dr. Channick.)

314. For the reasons discussed herein, Liquidia does not induce infringement of claims 7 and 8 of the '327 patent.

**7. Liquidia does not induce infringement of claims 9 and 10 because it does not instruct or encourage measuring FVC**

315. Claims 9 and 10 of the '327 patent require a “statistically significant improves [sic] of forced vital capacity” and an “improve[ment] [in] forced vital capacity (FVC) in the patient by at least 20 ml[,]” respectively. ('327 patent, Claim 9 and Claim 10.) This also requires measuring baseline FVC, measuring FVC after administration of YUTREPIA, and conducting statistical analyses on the changes in FVC.

316. The YUTREPIA label does not mention forced vital capacity. (*See generally* DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) Needless to say, neither the indications nor the administration instructions encourage healthcare providers or patients to measure FVC before or after treatment. (*Id.* at LIQ\_PH-ILD\_00126020-022.) The YUTREPIA label's description of the INCREASE study also omits any instruction or result related to FVC. (*Id.* at LIQ\_PH-ILD\_00126031-033.) When prescribing drugs like YUTREPIA, healthcare providers do not regularly measure FVC before and after treatment, aggregate the data, and then conduct

statistical analyses on the data when treating PH-ILD patients. (Anticipated Testimony of Dr. Channick.)

317. Dr. Nathan attempts to expand the scope of the YUTREPIA label by arguing that based on the contents of the YUTREPIA label and related INCREASE clinical data, physicians will administer YUTREPIA to PH-ILD patients with the intent to achieve the same results UTC observed in the INCREASE study. (Anticipated Testimony of Dr. Nathan.) More specifically, Dr. Nathan has argued that physicians would administer YUTREPIA to PH-ILD patients with the intended purpose and expectation that at least some of these PH-ILD patients would achieve improvements in forced vital capacity. (Anticipated Testimony of Dr. Nathan.) However, a physician administering YUTREPIA would not have the intent to achieve the same results as shown in the INCREASE study, or from any clinical study for that matter. (Anticipated Testimony of Dr. Channick.) Rather, a physician's intent in administering YUTREPIA would be to deliver the drug in a safe and efficacious manner to improve how the patient feels and functions. (Anticipated Testimony of Dr. Channick.) A physician's "intent" is not evidence of Liquidia's specific intent to induce infringement. (Anticipated Testimony of Dr. Channick.) A healthcare provider or patient would not review materials extraneous to the label, especially when the label itself provides sufficient instructions for the safe and efficacious administration of the drug. (Anticipated Testimony of Dr. Channick.) Because the YUTREPIA label already includes such instructions and does not include any instruction directing healthcare providers and patients to the INCREASE publication, doctors administering YUTREPIA would not review the INCREASE publication and would not intend or expect to improve FVC. (Anticipated Testimony of Dr. Channick.) Even if a doctor were to review material outside the YUTREPIA label, it would be of

their own volition and not based on an instruction or direction from Liquidia. (Anticipated Testimony of Dr. Channick.)

318. For the reasons discussed herein, Liquidia does not induce infringement of claims 9 and 10 of the '327 patent.

**D. Liquidia Does Not Induce Infringement of Claims 11, 14, 15, or 16 Because Liquidia Does Not Induce Infringement of Claim 1**

319. Dependent claims 11, 14, 15, and 16 directly or indirectly depend on independent claim 1 of the '327 patent. As described in Section VI.A above, Liquidia does not and will not induce infringement of claim 1. Because Liquidia does not have the specific intent to induce infringement of claim 1, Liquidia does not, and will not, have the specific intent to induce infringement of dependent claims 11, 14, 15, and 16 of the '327 patent.

**E. Liquidia's Marketing Materials Do Not Demonstrate Liquidia's Intent to Induce Infringement of Any of the Asserted Claims**

320. None of the alleged "marketing materials" Dr. Nathan cites instruct healthcare providers or patients to perform the steps of the dependent method of treatment claims in the '327 patent. (Anticipated Testimony of Dr. Channick.) The YUTREPIA Formulary Kit and YUTREPIA Product Dossier Dr. Nathan references, for instance, are not even directed to healthcare providers or patients; they are, instead, intended for payors. (DTX0130, Formulary Kit (LIQ\_PH-ILD\_00146970); DTX0131, Product Dossier (LIQ\_PH-ILD\_00146984).) And, of the marketing materials Dr. Nathan has cited that reference the INCREASE study, none instruct healthcare providers or patients to measure plasma NT-proBNP, exacerbations of interstitial lung disease, clinical worsening of interstitial lung disease, or FVC. (*See, e.g.*, DTX0135, Provider Presentation (LIQ\_PH-ILD\_00147196).) The remaining marketing materials Dr. Nathan cites do not contain any instructions for healthcare providers or patients to measure any of the secondary endpoints the dependent claims recite. (Anticipated Testimony of Dr. Channick.)

321. Dr. Nathan has opined that Liquidia's marketing materials illustrate to him that Liquidia expects doctors and patients to use YUTREPIA according to its label and that this demonstrates that Liquidia intends to market YUTREPIA in a manner that will instruct, encourage, recommend, and promote doctors and patients to infringe the Asserted Claims. (Anticipated Testimony of Dr. Nathan.) To support this position, Dr. Nathan has cited a YUTREPIA Formulary Kit and Product Dossier, which reference the INCREASE study. Mike Post, Liquidia's Vice President of Marketing, confirmed that the YUTREPIA Formulary Kit and YUTREPIA Product Dossier are documents that are intended to be provided to payors, and not practicing healthcare providers or patients (who are the alleged direct infringers identified by Dr. Nathan), following YUTREPIA's approval. (Anticipated Testimony of Dr. Channick.) Such documents are not the type of material that a physician would come across in their practice. (Anticipated Testimony of Dr. Channick.) Nor would these types of documents be provided to patients. (Anticipated Testimony of Dr. Channick.) Indeed, as Dr. Nathan confirmed, these materials would be provided to payors. Thus, because these documents are not intended for circulation amongst healthcare providers or patients, the YUTREPIA Formulary Kit and YUTREPIA Product Dossier do not support Dr. Nathan's opinion that Liquidia intends to market YUTREPIA in a manner that will instruct, encourage, recommend, and promote doctors and patients to infringe the Asserted Claims." (Anticipated Testimony of Dr. Channick.)

322. Included among the list of documents that Dr. Nathan has argued support his opinion regarding induced infringement, is a "CuraScript Pamphlet." (DTX0132 (LIQ\_PH-ILD\_00147068).) Mike Post confirmed that the CuraScript Pamphlet is intended for distribution to hospital pharmacies and not healthcare providers or patients. (Anticipated Testimony of Dr. Channick.) Thus, as is the case with the YUTREPIA Formulary Kit and the YUTREPIA Product



Dossier, this document fails to demonstrate that Liquidia intends to market YUTREPIA in a manner consistent with Dr. Nathan's theory of induced infringement. (Anticipated Testimony of Dr. Channick.)

323. While the "Provider Presentation" cited by Dr. Nathan references the INCREASE study, it does not instruct healthcare providers or patients to measure plasma NT-proBNP, exacerbations of interstitial lung disease, clinical worsening of interstitial lung disease, or FVC. (DTX0135 (LIQ\_PHILD\_00147196).) The remaining marketing materials Dr. Nathan has cited do not contain any instructions for healthcare providers or patients to measure any of the secondary endpoints the dependent claims recite, and therefore, like the materials described above, do not provide any evidence of an intent by Liquidia to induce infringement of the Asserted Claims. (DTX0133, Starter Kit Insert (LIQ\_PH-ILD\_00147176); DTX0134, Patient Brochure (LIQ\_PH-ILD\_00147178); DTX0135, Provider Presentation (LIQ\_PH-ILD\_00147196); DTX1058, Approved Email (LIQ\_PH-ILD\_00146942); DTX1059, Yutrepia Homepage Mockup 2 (LIQ\_PH-ILD\_00146936); DTX0130, Formulary Kit (LIQ\_PH-ILD\_00146970); DTX0131, Product Dossier (LIQ\_PHILD\_00146984); DTX1060, Liquidia Access (LIQ\_PH-ILD\_00146961); DTX1061, Sales Aid 2 (LIQ\_PH-ILD\_00147156); DTX0132, CuraScript Pamphlet (LIQ\_PHILD\_00147068); DTX1062, Sales Aid (LIQ\_PH-ILD\_00147141).)

**F. UTC Fails to Establish that Administration of YUTREPIA Infringes the Asserted Claims Under the Doctrine of Equivalents**

324. Dr. Nathan and UTC have taken the position that if any element of any of claims 1-11 and 14-19 are not literally satisfied when YUTREPIA is administered to PH-ILD patients, then all such elements are satisfied under the doctrine of equivalents. However, instead of performing an element-by-element analysis, Dr. Nathan has argued that his analysis with respect to literal infringement suffices to show infringement under the doctrine of equivalents.

325. UTC cites Liquidia's Proposed Label, regulatory filings, and marketing materials as evidence of infringement under the doctrine of equivalents. However, UTC's blanket statements about these documents fail to show how administering YUTREPIA to PH-ILD patients is insubstantially different from any element of the Asserted Claims. (Anticipated Testimony of Dr. Channick.) Nor has UTC or Dr. Nathan explained how these references demonstrate that YUTREPIA performs substantially the same function in the same way to achieve the same result as the Asserted Claims. (Anticipated Testimony of Dr. Channick.)

326. UTC claims that the YUTREPIA label demonstrates that YUTREPIA will infringe under the doctrine of equivalents. However, UTC has not explained how the label's disclosure demonstrates that YUTREPIA is insubstantially different, or performs substantially the same function in the same way to achieve the same result as the Asserted Claims and therefore has not met its burden under the doctrine of equivalents.

327. UTC makes the same claims about Liquidia's marketing materials, but also fails to perform the element-by-element analysis to establish that the marketing materials demonstrate that YUTREPIA is insubstantially different, or performs substantially the same function in the same way to achieve the same result as the Asserted Claims. Thus, UTC has not met its burden under the doctrine of equivalents.

328. UTC also claims that Liquidia's regulatory filings show that YUTREPIA infringes the Asserted Claims of the '327 patent under doctrine of equivalents. These regulatory filings include the LTI-102 study, and the LTI-301, INSPIRE, study. The LTI-102 study evaluated the bioavailability and safety of YUTREPIA relative to Tyvaso® in *healthy subjects*. The results were published in Roscigno R., et. Al., *Comparative bioavailability of inhaled treprostinil administered as LIQ861 and Tyvaso® in healthy subjects*, Vascular Pharm. 138:106840 (2021)

(“Roscigno 2021”). Dr. Nathan has taken the position that this bioavailability data is enough to show infringement under the doctrine of equivalents. (Anticipated Testimony of Dr. Nathan.) Specifically, Dr. Nathan has opined that Roscigno 2021 demonstrated comparable bioavailability and similar tolerability when these two products were administered to *healthy adults*, but he provides no analysis as to how these findings support finding an insubstantial difference between an element of the accused product or process and claim elements directed to PH-ILD patients. (Anticipated Testimony of Dr. Channick.) Moreover, the data Dr. Nathan points to is “bioavailability data,” which simply indicates that blood levels of treprostinil administered via YUTREPIA were comparable to blood levels of treprostinil administered via Tyvaso. Further, Dr. Nathan and UTC have provided no support, based on bioavailability data in this 2021 article, for a determination that any element in YUTREPIA will perform substantially the same function in the same way to achieve the same results as any element of the Asserted Claims. (Anticipated Testimony of Dr. Channick.)

329. Dr. Nathan has also relied on the INSPIRE study, also known as the LTI-301 study, whose results were published in a 2022 research article in *Pulmonary Circulation*, various statements in Liquidia’s New Drug Application and the results of its bioavailability comparison to Tyvaso®, and Liquidia’s 2024 J.P. Morgan Healthcare Conference Presentation, to support a doctrine of equivalents argument. (Anticipated Testimony of Dr. Nathan.) This argument is similarly flawed. Dr. Nathan has not explained how these materials relate to demonstrating an insubstantial difference between an element of the accused product or process and claim element(s) or to a finding that any element YUTREPIA performs the same function in the same way to achieve the same results as any element of the Asserted Claims.

330. Dr. Nathan has also cited Liquidia's NDA, specifically Liquidia's statement to the FDA that "[t]he established comparable bioavailability of LIQ861 [Yutrepia] to Tyvaso facilitates a simple transition for patients to LIQ861 [Yutrepia] from Tyvaso and provides physicians with a titration methodology similar to the well-known approach for Tyvaso[.]" and the results that Liquidia presented from its bioavailability study. (Anticipated Testimony of Dr. Nathan.) Liquidia's bioavailability comparison simply indicates that blood levels of treprostinil administered via YUTREPIA were comparable to blood levels of treprostinil administered via Tyvaso.<sup>1</sup> Dr. Nathan provides no support, based on Liquidia's NDA, to demonstrate an insubstantial difference between an element of the accused product or process and claim elements or for a determination that YUTREPIA will perform substantially the same function in the same way to achieve the same results as any of the Asserted Claims. (Anticipated Testimony of Dr. Channick.)

331. Dr. Nathan has also cited Liquidia's statement during a January 10, 2024 J.P. Morgan Healthcare Conference Presentation, that YUTREPIA has "[c]omparable pharmacokinetics to Tyvaso®." The comparison of pharmacokinetics between YUTREPIA and Tyvaso simply relates to how the body handles (*e.g.*, absorbs, distributes, metabolizes, and excretes) the substances for the duration of exposure. (Anticipated Testimony of Dr. Channick.) Dr. Nathan provides no support, based on Liquidia's 2024 statement relating to comparable pharmacokinetics, for finding insubstantial differences between an element of the accused product or process and any claim elements or a determination that YUTREPIA will perform substantially

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<sup>1</sup> To the extent UTC argues that bioavailability data is sufficient to prove infringement, then treprostinil blood level data would also be sufficient to establish the invalidity of the Asserted Claims.

the same function in the same way to achieve the same results as any of the Asserted Claims. (Anticipated Testimony of Dr. Channick.)

332. Dr. Nathan's arguments lack any element-by-element support for his assertions regarding infringement under the doctrine of equivalents. Instead, Dr. Nathan has merely relied on the fact that Liquidia is seeking FDA approval for YUTREPIA based on the INCREASE study, citing articles and statements which conclude that the two products demonstrate comparable bioavailability, similar tolerability, and comparable pharmacokinetics, to support UTC's infringement position under the doctrine of equivalents. Dr. Nathan and UTC have argued that Dr. Channick does not point to any data or other evidence to suggest that administering YUTREPIA to PH-ILD patients according to the YUTREPIA label would not improve exercise capacity, increase 6MWD, reduced plasma concentrations of NT-proBNP, reduce exacerbations, reduce clinical worsening events, and improve FVC at levels sufficient to satisfy Asserted Claims 1-10 and 17-19 of the '327 patent. (Anticipated Testimony of Dr. Nathan.) However, UTC bears the burden of proof with respect to infringement and UTC has not demonstrated that administering YUTREPIA according to the label will infringe any of the Asserted Claims, under the doctrine of equivalents or otherwise. (Anticipated Testimony of Dr. Channick.)

**G. The ASCENT Study Does Not Establish Direct or Induced Infringement of Any Asserted Claim**

333. Dr. Nathan has argued that Liquidia directly infringes and induces infringement of the '327 patent by conducting the ASCENT study. (Anticipated Testimony of Dr. Nathan.) Specifically, Dr. Nathan has argued that doctors and patients that participate in ASCENT are directly infringing the Asserted Claims because the trial protocol for ASCENT requires YUTREPIA to be administered in an infringing manner consistent with the YUTREPIA label and by directing the doctors and patients in ASCENT to administer YUTREPIA according to its trial

protocol, Liquidia both directly infringes the Asserted Claims and induces the infringement of participating doctors and patients.

334. ASCENT does not establish direct or induced infringement of any Asserted Claim for at least the following reasons: (1) the ASCENT study does not make Liquidia a direct infringer of any of the Asserted Claims because Liquidia does not perform any step of the claimed methods; (2) ASCENT does not establish infringement because it is protected by the safe harbor; (3) Dr. Nathan relies solely on the ASCENT protocol and not actual data from the study, and thus cannot establish infringement of any Asserted Claim; and (4) ASCENT is a clinical trial that will be terminated and, as such, any alleged infringement will not be on-going. Furthermore, Dr. Nathan's reliance on the ASCENT protocol alone reinforces that the Asserted Claims are invalid under inherent anticipation.

335. Liquidia's ASCENT study is an open-label, multicenter study evaluating the safety and tolerability of YUTREPIA in patients with PH-ILD. (DTX0158, First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at LIQ\_PH-ILD\_00147611.) ASCENT is also referred to by its protocol number, LTI-401, and its full title is "An Open-Label Prospective Multicenter Study to Evaluate Safety and Tolerability of Dry Powder Inhaled Treprostinil in Pulmonary Hypertension[.]" (*Id.*) The stated primary objective for ASCENT is to "evaluate the safety and tolerability of LIQ861 [YUTREPIATM] in subjects with WHO Group 1 & 3 Pulmonary Hypertension (PH)." (*Id.*) The exploratory objectives of ASCENT are to "assess the effects of LIQ861 [YUTREPIATM] on exercise capacity, functional class, relevant biomarkers, and imaging assessments." (*Id.*) The original protocol for ASCENT is dated August 21, 2023; the first amended protocol, which did not change the dosing or administration, is dated October 3, 2023; and the actual study start date was December 28, 2023. (DTX0116, Original ASCENT Protocol

(LIQ\_PH-ILD\_00124867) at LIQ\_PH-ILD\_00124868; DTX0158, First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at LIQ\_PH-ILD\_00147608; DTX0305, ASCENT at Clinical Trials (UTC\_PH-ILD\_000395) at UTC\_PH-ILD\_000396.)

336. Liquidia discussed conducting a study evaluating the safety and tolerability of YUTREPIA in patients with PH-ILD at least as early as May 20, 2023, at its PH-ILD Advisory Board meeting. (DTX0111, LIQ\_PH-ILD\_00122627 (May 20, 2023 PH-ILD Advisory).) At the meeting, Dr. Rajeev Saggar held a discussion regarding Liquidia’s PH-ILD clinical program. (*Id.* at LIQ\_PH-ILD\_00122648.) The doctors on the advisory board all expressed interest in this study for various reasons, including interest in dosing titration using a dry powder inhaler and interest in the pulmonary functional test values achieved with YUTREPIA. (*Id.* at LIQ\_PH-ILD\_00122649.) Dr. Ryan specifically noted that it would be “very important” for YUTREPIA to replicate the pulmonary functional test values because he was “concerned that we have never replicated the FEV/FVC changes from INCREASE.” (*Id.*)

**1. The ASCENT Study does not make Liquidia a direct infringer of any Asserted Claim**

337. Dr. Nathan has argued that by directing the doctors and patients in ASCENT to administer Yutrepia according to its trial protocol, Liquidia both *directly* infringes the Asserted Claims and induces the infringement of participating doctors and patients. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan asserts that Liquidia *directly* infringes the Asserted Claims because the doctors and patients involved in ASCENT operate under the supervision and express instructions of Liquidia. (Anticipated Testimony of Dr. Nathan.) However, a party is liable for *directly* infringing a method claim if it *practices each step of a patent claim* in the United States and it is the physicians and patients who perform and enroll in the study—not Liquidia. Liquidia is a company and does not perform any step of the method claimed in the Asserted Claims.

Nevertheless, Dr. Nathan has argued that the physicians and patients involved in ASCENT are under Liquidia's "control" such that Liquidia would be considered a direct infringer. However, even if healthcare providers and patients "follow" a clinical trial protocol, they are not automatically under the sponsor's "control." (Anticipated Testimony of Dr. Channick.) Dr. Nathan admitted that when he is involved in a clinical study, he is not under the "control" of the sponsoring company. (Nathan Depo. Tr. at 149:22-150:7.) In any event, Liquidia is not performing any claimed step and cannot be a direct infringer. (Anticipated Testimony of Dr. Channick.) Accordingly, the ASCENT study does not establish Liquidia as a direct infringer of any Asserted Claim.

**2. The ASCENT Study is not evidence of infringement because it is protected by the safe harbor**

338. As a threshold matter, the ASCENT study does not constitute or provide evidence of infringement (direct or induced) of any Asserted Claim of the '327 patent because activities performed under the ASCENT study are protected by the safe harbor. Activities are protected under the safe harbor if they are reasonably related to the development and submission of information to the FDA. Here, Liquidia submitted information generated by the ASCENT study to the FDA. Accordingly, the ASCENT study falls squarely into the safe harbor because it is "reasonably related"—and in fact, directly related—to the submission of information to the FDA.

339. [REDACTED]

[REDACTED]

[REDACTED]. (DTX0163, LIQ\_PH-ILD\_00148561

(highlighting added).)



[REDACTED]

340.

[REDACTED]

[REDACTED]

[REDACTED] (DTX0162, LIQ\_PH-ILD\_00148554 at

LIQ\_PH-ILD\_00148558, -559, -560 (highlighting added to all).)

[REDACTED]

[REDACTED]

\*\*\*

[REDACTED]

\*\*\*

[REDACTED]

341. [REDACTED]

[REDACTED]

[REDACTED] (See DTX0681–DTX1045, LIQ\_PH-ILD\_00147815–LIQ\_PH-ILD\_00148500; Anticipated Testimony of Dr. Channick.) [REDACTED]

[REDACTED]

[REDACTED] (Anticipated Testimony of Dr. Channick.)

342. Because Liquidia has submitted and will continue to submit safety data and other information from the ASCENT study to the FDA, the ASCENT study is reasonably related to the submission of information to the FDA and thus non-infringing under the safe harbor.

343. Dr. Nathan has applied the incorrect standard when evaluating whether the ASCENT study is protected by the safe harbor. He has argued that Liquidia is not relying on ASCENT to get FDA approval for Yutrepia in PH-ILD. But the correct standard is whether the ASCENT study is reasonably related to the development and submission of information to the FDA (it is)—not whether the study is being “relied upon” for FDA approval. (Anticipated Testimony of Dr. Channick.) Based on this misinterpretation, Dr. Nathan and UTC have reached the conclusion that the ASCENT study does not qualify for safe harbor protection and, as a result there is infringement by the ASCENT study. (Anticipated Testimony of Dr. Nathan.)

344. Dr. Nathan has further asserted that the ASCENT study is being performed primarily for marketing purposes and is entirely unrelated to Liquidia’s efforts to obtain regulatory approval for the use of Yutrepia to treat PH-ILD patients. (Anticipated Testimony of Dr. Nathan.) However, whether the ASCENT study is related to Liquidia’s “efforts to obtain regulatory approval” is not the standard for safe harbor protection; instead, the proper inquiry is whether the ASCENT study is reasonably related to the development and submission of information to the FDA (it is). Dr. Nathan’s reliance on an incorrect standard renders his opinion incorrect. (Anticipated Testimony of Dr. Channick.)

345. Further, once the safe harbor is found to apply, the underlying purposes of the activity are irrelevant. Because information from the ASCENT study was and will continue to be submitted to the FDA, the study is protected by the safe harbor, and the underlying purposes of the study are not considered. (Anticipated Testimony of Dr. Channick.)

346. Similarly, it does not matter whether the ASCENT study was intended to showcase the product profile of Yutrepia for medical providers or that ASCENT has no regulatory status in regards to the FDA’s consideration for approval or indication of PH-ILD for YUTREPIA. The

underlying motivations or attendant consequences of the study, such as showcasing the product profile to providers, are irrelevant once the safe harbor is found to apply (as it does here). Additionally, having “regulatory status” with the FDA is not a prerequisite for the safe harbor to apply, and that courts simply ask whether the activity is reasonably related to the development or submission of information to the FDA (as the ASCENT study here is).

347. For the foregoing reasons, the ASCENT study is protected by the safe harbor, and thus cannot infringe any Asserted Claim of the ’327 patent. (Anticipated Testimony of Dr. Channick.)

**3. UTC Cannot Establish Infringement of the Asserted Claims by relying on the ASCENT Protocol Alone**

348. Dr. Nathan has argued that the ASCENT study infringes the Asserted Claims and that concrete data from ASCENT is not required to establish infringement. (Anticipated Testimony of Dr. Nathan.) This position assumes that infringement occurs if the study is run and is therefore insufficient to establish direct or induced infringement of the Asserted Claims.<sup>2</sup> (Anticipated Testimony of Dr. Channick.) The ASCENT protocol is not an act of “administering” treprostinil to a PH-ILD patient, and moreover, the protocol does not evidence “improving exercise capacity” in a PH-ILD patient as required by claim 1. (See ’327 patent at Claim 1.) Because the

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<sup>2</sup> Dr. Nathan has relied on the ASCENT protocol, including its dosing regimen and patient population, to conclude that running the study will necessarily and inevitably meet each claim limitation, including those requiring statistical significance. While Liquidia disagrees with his infringement opinion based on the ASCENT protocol for the reasons explained herein, to the extent Dr. Nathan relies on the ASCENT protocol describing a patient population and dosing regimen to prove direct infringement, then Dr. Nathan’s opinion reinforces Liquidia’s position that the Asserted Claims are invalid as inherently anticipated because the ASCENT protocol has patient population (PH-ILD), route of administration (inhaled treprostinil) and dosing regimen as prior art references Faria-Urbina 2018, the 2009 Tyvaso® label, the 2017 INCREASE Study Description, and Agarwal 2015.

ASCENT protocol does not evidence direct infringement by anyone, then it does not evidence direct infringement for the remaining Asserted Claims, which all depend directly or indirectly from claim 1.<sup>3</sup> (Anticipated Testimony of Dr. Channick.) Because the ASCENT protocol does not evidence direct infringement, it also does not support Dr. Nathan's opinion that it provides evidence of Liquidia's induced infringement of the Asserted Claims. (Anticipated Testimony of Dr. Channick.)

349. While Dr. Nathan has argued that preliminary data from ASCENT evidences infringement of claim 1, there is no data, preliminary or otherwise, that UTC can claim supports its infringement arguments with respect to the dependent claims. Because the following asserted dependent claims require either a "statistically significant" result (claims 2, 4, 6, 7-8, 9-10) and/or a particular result that must be measured (claims 3, 5, 8, 10, 17-19), a POSA would have understood that each of these claims require a healthcare provider to actually collect data for the claimed endpoint. (Anticipated Testimony of Dr. Channick.) Dr. Nathan has argued that the endpoints forming the basis for the Asserted Claims "should be" or "will be" measured in the future. (Anticipated Testimony of Dr. Nathan.) However, this is not enough to establish infringement as concrete data is needed to show that each and every step of claims 2-10 and 17-19 is satisfied. (Anticipated Testimony of Dr. Channick.)

350. Moreover, for the claims requiring a "statistically significant" result (claims 2, 4, 6, 7, 9), a POSA would have understood that the healthcare provider must take the additional steps

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<sup>3</sup> In contrast to inherent anticipation, infringement is a different inquiry and requires one to actually perform the claimed method. Thus, the 2017 INCREASE Study Description is sufficient to establish inherency for invalidity purposes, but the ASCENT protocol is insufficient to establish infringement because the method steps of the Asserted Claims are not performed and no outcome measurements are provided.

of treating multiple patients, aggregating the data collected from the patients, and then running a statistical analysis. (See D.I. 149 at 6 (Claim Construction Order stating that “finding statistical significance requires data from multiple patients”; see also Deng Depo. Tr. at 163:19-164:1.) The ASCENT protocol does not disclose performing these steps. (See generally DTX0116, Original ASCENT Protocol (LIQ\_PH-ILD\_00124867); DTX0158, First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607).) In fact, the ASCENT protocol expressly states that “[REDACTED]

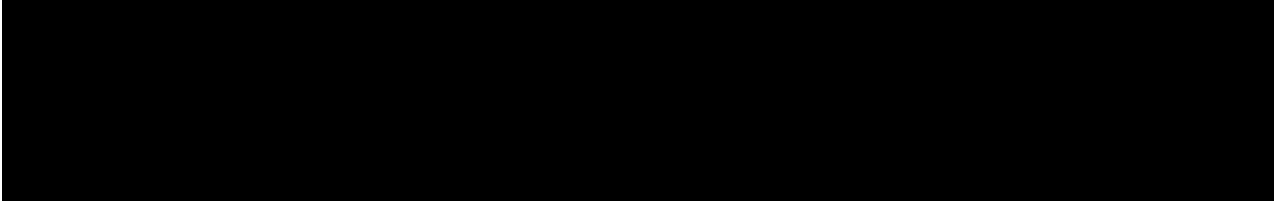
[REDACTED]

[REDACTED]

[REDACTED]

(DTX0158, First Amended ASCENT Protocol at LIQ\_PH-ILD\_00147616 (highlighting added).)

351. The only specific reference to statistics in the ASCENT protocol is descriptive statistics, as shown below:



(*Id.* at LIQ\_PH-ILD\_00147656 (highlighting added).)

352. Chunqin Deng, a statistician and named inventor of the '327 patent, testified that the claimed “statistical[] significan[ce]” referred to p-values and classical inferential statistics—not descriptive statistics as disclosed in the ASCENT protocol. (Deng Depo. Tr. at 120:4-14.) Thus, the ASCENT protocol’s reference to “descriptive statistics” does not satisfy the “statistically significant” limitations in claims 2, 4, 6, 7, and 9. (Anticipated Testimony of Dr. Channick.)

353. The ASCENT protocol alone is not sufficient to establish infringement of any asserted claim. (Anticipated Testimony of Dr. Channick.) UTC cannot impute infringement by assuming that running the ASCENT study will lead to the claimed results.

354. Dr. Nathan has attempted to draw parallels between the ASCENT study and UTC’s INCREASE study, but the two are very different studies. (Anticipated Testimony of Dr. Channick.) First, INCREASE was a double-blinded, placebo-controlled study with approximately 314 subjects, whereas ASCENT is an open-label study with no placebo and approximately 60 patients. (DTX0401, Feb. 15, 2017 INCREASE Protocol (UTC\_PH-ILD\_105083) at UTC\_PH-ILD\_105102; DTX0158, First Amended ASCENT Protocol at LIQ\_PH-ILD\_00147626.) Second, INCREASE evaluated efficacy as a primary endpoint, [REDACTED] Specifically, INCREASE’s primary endpoint was “[t]o evaluate the change in 6-minute walk distance (6MWD) measured at peak exposure from Baseline to Week 16[,]” while ASCENT’s primary endpoint is safety and tolerability—*i.e.*, “[REDACTED]

[REDACTED]

[REDACTED] (DTX0401, Feb. 15, 2017 INCREASE Protocol at UTC\_PH-ILD\_105086; DTX0158, First Amended ASCENT Protocol at LIQ\_PH-ILD\_00147627.) INCREASE also includes time to clinical worsening as an exploratory endpoint and exacerbations of underlying lung disease as a safety endpoint, [REDACTED]

[REDACTED] (DTX0401, Feb. 15, 2017 INCREASE Protocol at UTC\_PH-ILD\_105101-102; DTX0158, First Amended ASCENT Protocol at LIQ\_PH-ILD\_00147615-616, -627.)

355. Dr. Nathan has argued that the overlapping endpoints between ASCENT and INCREASE demonstrate Liquidia's expectation that YUTREPIA will perform comparably in ASCENT to what UTC demonstrated for Tyvaso in INCREASE. (Anticipated Testimony of Dr. Nathan.) However, YUTREPIA and Tyvaso are two different formulations. Indeed, if the same results were expected, then there would be no purpose in performing a clinical trial at all.

#### **4. ASCENT is a clinical trial that is expected to conclude in 2026**

356. Dr. Nathan has argued that by performing its ongoing ASCENT study, Liquidia is infringing—*and will continue to infringe*—each and every Asserted Claim of the '327 patent. (Anticipated Testimony of Dr. Nathan.) However, Dr. Nathan has not addressed the fact that the ASCENT study is a clinical trial that will be terminated once the PH-ILD portion is complete. As noted on the ClinicalTrials.gov website, the ASCENT study is expected to last approximately 2.5 years and end around June 2026. (DTX0305, ASCENT at Clinical Trials (UTC\_PH-ILD\_000395) at UTC\_PH-ILD\_000401.) Accordingly, even if ASCENT infringes the Asserted Claims (it does not), any infringement is expected to stop in 2026.



357. Dr. Nathan has also asserted that Liquidia chose to initiate ASCENT after being sued in this lawsuit and learning of UTC's infringement allegations. However, this ignores the fact that the original ASCENT protocol is dated August 21, 2023, and the first amended ASCENT protocol is dated October 3, 2023. (DTX0116, Original ASCENT Protocol (LIQ\_PH-ILD\_00124867) at LIQ\_PH-ILD\_00124868; DTX0158, First Amended ASCENT Protocol at LIQ\_PH-ILD\_00147608.) Additionally, the ASCENT study was first posted on ClinicalTrials.gov on November 13, 2023. (DTX0305, ASCENT at Clinical Trials at UTC\_PH-ILD\_000402.) The '327 patent did not issue until November 28, 2023, and was not asserted in this litigation until November 30, 2023—*i.e.*, **after** the planning for the ASCENT study was significantly underway and the clinical trial design, including the dosing regimen and patient population, was established. Thus, Liquidia initiated planning and design of the ASCENT study months before the '327 patent issued. (Anticipated Testimony of Dr. Channick.)

358. Further, the ASCENT study is not referenced in the proposed label for YUTREPIA. (See generally DTX0118, YUTREPIA Label (LIQ\_PH-ILD\_00126017).) Dr. Nathan has relied on the ASCENT protocol for its use of endpoints including NT-proBNP and FVC. (Anticipated Testimony of Dr. Nathan.) This underscores the absence of those parameters from the YUTREPIA proposed label and confirms that Liquidia has no intent to instruct healthcare providers and/or patients to measure NT-proBNP or FVC, as required by certain Asserted Claims.

#### **H. Liquidia Does Not Willfully Infringe The '327 Patent**

359. Liquidia did not willfully infringe the '327 patent before its issuance. The evidence on which UTC relies to establish willfulness merely demonstrates Liquidia's preparation for, and filing of, its 505(b)(2) application. Without more, UTC cannot prove willfulness. Liquidia's ASCENT trial, moreover, is protected under the safe harbor exception, was initiated before

issuance of the '327 patent, and, thus, cannot be used to establish willful infringement. Taken together, Liquidia's actions prior to November 28, 2023, do not establish willful infringement.

360. Liquidia first proposed adding a PH-ILD indication to its YUTREPIA label in April 2022 and then amended its NDA to include a PH-ILD indication in July 2023. (Liquidia Meeting Request (DTX0125 (LIQ\_PH-ILD\_00134026) at LIQ\_PH-ILD\_00134029; DTX0032, YUTREPIA Label (LIQ\_PH-ILD\_00000896); *see also* DTX1299, Liquidia July 24, 2023 letter to FDA(LIQ\_PH-ILD\_00091022).) The '327 patent did not issue until November 28, 2023. ('327 patent (cover).) Liquidia cannot willfully infringe a patent that did not exist.

361. UTC cites Liquidia's awareness and use of the INCREASE trial data as evidence of willful infringement. But this ignores that Liquidia's actions with respect to the INCREASE trial were tied to the regulatory requirements of the 505(b)(2) pathway for YUTREPIA. And awareness of a clinical trial is not infringement of a non-existent patent claim. Further, awareness of the INCREASE trial is not evidence of infringement of the '327 patent when it issued. The INCREASE trial is not a patent.

362. As UTC notes, on May 20, 2023, before the '327 patent issued, Liquidia held a PH-ILD Advisory Board meeting to discuss the potential use of YUTREPIA to treat PH-ILD patients. (DTX0111, May 20, 2023 PH-ILD Advisory (LIQ\_PH-ILD\_00122627).) UTC focuses on Dr. Franck Rahaghi's presentation on data from the INCREASE trial and conveniently ignores that the INCREASE trial was only one of several topics discussed during the advisory board meeting, which also included a discussion of case studies of patients with PH-ILD, the results of the INSPIRE study, the PERFECT trial, and Liquidia's PH-ILD clinical program. (*Id.* at LIQ\_PH-ILD\_00122629.) Dr. Rajeev Saggar explained that Dr. Rahaghi was invited to talk about the

INCREASE trial at the Advisory Board meeting because, “It’s relevant to our interest.” (Rajeev Saggar Depo. Tr. at 195:8-11.)

363. Nor does the fact that Liquidia referenced the INCREASE trial in its amendment for the PH-ILD indication evidence of willful infringement as it is permitted under the 505(b)(2) regulatory pathway. Dr. Saggar’s testimony that Liquidia “deserved” to rely on the INCREASE trial is consistent with the process for FDA approval. Indeed, Dr. Rajeev Saggar clarified that he believed the reason Liquidia deserved to rely on the INCREASE study results was because it “is part of the 505(b)(2) process, and we have followed the regulatory statutes and done the proper work.” (*Id.* at 197:12-23.)

364. Moreover, the INCREASE clinical trial does not align precisely with the claims of the ’327 patent because the claims do not cover the specific inclusion and exclusion criteria used in the INCREASE study and thus is not evidence of willful infringement.

365. UTC’s arguments regarding willful infringement ignore the regulatory context in which Liquidia operated in and mischaracterizes the nature and purpose of Liquidia’s conduct with respect to the pending ’061 application.

366. Liquidia’s decision to amend its 505(b)(2) application to add the PH-ILD indication was made to avoid unnecessary delays from the FDA regulatory process. When asked why Liquidia was trying to file its application before the ’327 patent issued, Dr. Rajeev Saggar, Liquidia’s CMO, testified that Liquidia wanted to submit its amendment before the patent was listed in the Orange Book in order to avoid the statutory 30-month stay from the FDA. (Rajeev Saggar Depo. Tr. at 109:19-110:23.) Roger Jeffs’ email to the Liquidia Board and the various SEC filings UTC references merely acknowledge this important regulatory decision and is not a comment on whether or not Liquidia could potentially infringe on a patent stemming from the ’061

application. (DTX1296, Jeffs Email to Board (LIQ\_PH-ILD\_00113806); DTX 1297, June 30, 2023 FORM 10-Q (LIQ\_PH-ILD\_00142130) at -00142182, -00142193, -00142196; DTX1298, Sept. 30, 2023 FORM 10-Q (LIQ\_PH-ILD\_00142363) at -00142415-16, -00142426-27, -00142430.)

367. UTC also claims that Liquidia’s decision to initiate the ASCENT trial after the issuance of the ’327 patent evidences bad faith. As discussed in Section VI.G above, the ASCENT study is protected by Safe Harbor and does not infringe the ’327 patent. Additionally, as discussed in paragraph 341, Liquidia discussed initiating a clinical trial like ASCENT prior to the issuance of the ’327 patent.

368. UTC’s remaining willful infringement allegations regard activities that are wholly unrelated to the ’327 patent and therefore cannot, on their face, support a finding of willful infringement. Moreover, UTC’s characterization of Liquidia’s conduct as evidence of “bad faith” is irrelevant and is untethered from the legal standard for willful infringement. Nevertheless, each allegation is addressed below.

369. UTC’s claim that Liquidia presents a “practicing the prior art” defense is baseless as Liquidia does not rely on any such defense to establish non-infringement. As discussed in § VI.A, Liquidia lacks the specific intent to induce direct infringement because its proposed label for YUTREPIA, to include the PH-ILD indication, simply reflects activities already present in the public domain. This is a specific intent issue, not a “practicing the prior art” issue.

370. UTC’s allegations that Liquidia’s inequitable conduct allegation is baseless is similarly unfounded. As further discussed in § XII below, Liquidia’s inequitable conduct claim is supported by deposition testimony from Mr. Snader and Mr. Maebius. The fact that Liquidia did

not have this deposition testimony or the benefit of the discovery process at the time it pled this allegation does not (as UTC argues) render it baseless.

371. Finally, Liquidia's engagement and representation of individuals engaged by UTC also does not establish willful infringement. As noted above, activities unrelated to the '327 patent cannot not establish willful infringement.

## **VII. PRIORITY DATE**

372. The '327 patent claims priority to Provisional Application No. 63/011,810, filed April 17, 2020 (the "'810 provisional") and Provisional Application No. 63/160,611, filed March 12, 2021 (the "'611 provisional"). ('327 patent at Cover.)

373. The '810 provisional, which is listed on the cover of the '327 patent under the heading, "Related U.S. Application Data," is entitled "TREATMENT FOR INTERSTITIAL LUNG DISEASE." ('327 patent at Cover; DTX0375, '810 provisional.) The inventors listed on the '810 provisional are Leigh Peterson, Peter Smith, and Chunqin Deng. (DTX0375, '810 provisional.)

374. Because UTC has taken the position that the invention of the '327 patent was not conceived until the unblinding of the INCREASE study (Peterson Depo. Tr. at 160:18-161:16; Deng Depo. Tr. at 128:4-129:23; Smith Depo. Tr. at 237:9-18), the '810 provisional does not provide adequate written description and enablement support for the claims of the '327 patent. Specifically, the '810 provisional does not include any data supporting the claimed improvements in exercise capacity, NT-proBNP, or clinical worsening events, which is data that would have been disclosed as the results of a Phase III clinical trial. (Anticipated Testimony of Dr. Channick; Peterson Depo. Tr. at 170:19-174:1; Deng Depo. Tr. at 147:16-149:3.) It does not, for example, include the INCREASE protocol or results. (Anticipated Testimony of Dr. Channick.)

375. All three '327 patent inventors have testified that they first possessed the invention of improving exercise capacity in a PH-ILD patient using inhaled treprostinil when the results of the INCREASE Phase III clinical trial were unblinded. Inventor Dr. Peter Smith testified that he and UTC only understood they were in possession of a method of improving exercise capacity in PH-ILD patients using inhaled treprostinil “[a]t the time of unblinding . . . in February of 2020.” (Smith Depo. Tr. at 237:9-18.) Inventors Dr. Leigh Peterson and CQ Deng agreed, testifying that they did not possess the invention claimed in the '327 patent until the conduct and results of the INCREASE trial were obtained.” (Peterson Depo. Tr. at 160:18-161:16; Deng Depo. Tr. at 128:4-129:23.) Thus, based on the testimony of the '327 patent inventors, the inventors believe they did not invent the claimed method of the '327 patent until the INCREASE trial was completed and results were known. (Anticipated Testimony of Dr. Channick.)

376. The INCREASE study is not mentioned at all in the '810 provisional and cannot be used by a POSA to determine whether the inventors were in possession of the '327 patent claims.

377. The '810 provisional includes three independent claims, none of which claim a method of treating PH-ILD. Claim 1 is directed to “[a] method of treating interstitial lung disease (ILD) or pulmonary fibrosis in a subject,” claim 2 is directed towards “[a] method of reducing pulmonary function decline in a subject with interstitial lung disease (ILD) or pulmonary fibrosis,” and claim 3 is directed to “increasing forced vital capacity (FVC) in a subject suffering from ILD or pulmonary fibrosis.” (DTX0375, '810 provisional (UTC\_PH-ILD\_069472) at UTC\_PH-ILD\_069503.)

378. None of the conditions being treated by the claims filed with the '810 provisional are pulmonary hypertension, or PH-ILD. (Smith Depo. Tr. at 72:8-18.) A POSA would

understand the claimed methods of treatment, in the '327 patent, to be treating PH-ILD. (Anticipated Testimony of Dr. Channick.)

379. The '810 provisional includes Examples 1 and 2 that are present and unchanged in the later '611 provisional and the issued '327 patent. (DTX0375, '810 provisional at UTC\_PH-ILD\_069495–501; Smith Depo. Tr. at 66:3-67:9, 68:4-9; Peterson Depo. Tr. at 172:5-13, 173:14-22.) The '810 provisional does not include the later Examples 3, 4, and 5 contained in the '327 patent, which were added in the March 12, 2021, filing of the '611 provisional. (DTX0376, '611 provisional at UTC\_PH-ILD\_069589–620; Deng Depo. Tr. at 150:8-13; Smith Depo. Tr. at 71:4-9; Peterson Depo. Tr. at 172:23-174:1.)

380. Example 1 describes “Inhaled Treprostinil Results on Underlying Lung Disease.” (DTX0375, '810 provisional at UTC\_PH-ILD\_069495; DTX0376, '611 provisional at UTC\_PH-ILD\_069584; '327 patent at 22:10-11.) Example 1 evaluates “[a]n exacerbation of underlying lung disease,” and defines exacerbations of underlying lung disease as acute, clinically significant, respiratory deteriorations characterized by evidence of new widespread alveolar abnormality. (DTX0375, '810 provisional at UTC\_PH-ILD\_069495.)

381. Patients were administered inhaled treprostinil or placebo over a 16-week period, beginning at a dose of 3 breaths (18 mcg) four times daily, with escalation allowed every three days to a target dose of 9 breaths (54 mcg) four times daily and a maximum of 12 breaths (72 mcg), as clinically tolerated. (DTX0375, '810 provisional at UTC\_PH-ILD\_069496 [0081].) Example 1 mentions several endpoints, including 6-minute walk distance (“6MWD”), plasma NT-proBNP concentrations, time to clinical worsening, and pulmonary function tests; however, it does not disclose any results for these endpoints. (DTX0375, '810 provisional at UTC\_PH-ILD\_069496 [0082].) Importantly, Example 1 does not provide any data for these endpoints.

(Peterson Depo. Tr. at 170:19-174:1; Deng Depo. Tr. at 147:16-149:19; Smith Depo. Tr. at 58:23-59:8; Maebius Depo. Tr. at 154:2-155:12.)

382. Example 1 provides results only for the reduction in exacerbations of underlying lung disease and improvements in forced vital capacity (FVC”). (DTX0375, ’810 provisional at UTC\_PH-ILD\_069496–501.) This data addresses lung diseases but is not directed to outcomes on PH-ILD. (Anticipated Testimony of Dr. Channick.)

383. Data for FVC, however, addresses lung function and is used as a safety measure, but is not used as a measure of PH-ILD, or exercise capacity in PH-ILD patients. (Anticipated Testimony of Dr. Channick; Smith Depo. Tr. at 55:23-57:1; Waxman Depo. Tr. at 154:18-155:3.)

384. FVC was used solely as a safety measure in the INCREASE study with corresponding data presented in Example 1, and it was not a measure of efficacy or exercise capacity. (Smith Depo. Tr. at 55:23-57:1; Waxman Depo. Tr. at 154:15-155:3.)

385. Example 2, which is a prophetic example, also does not include any actual results with respect to improvements in exercise capacity, six-minute walk distance, NT-proBNP, or clinical worsening events. (Maebius Depo. Tr. at 152:7-153:2; Deng Depo. Tr. at 149:4-150:7; Smith Depo. Tr. at 61:7-62:3.) Example 2 was not intended to study patients with PH and interstitial lung disease, but rather intended to assess patients with interstitial lung disease. (Smith Depo. Tr. at 70:13-20.)

386. Claim 1 of the ’327 patent requires a method of improving exercise capacity in patients with PH-ILD. (’327 patent at Claim 1.) There is no data in the ’810 provisional indicating to a POSA that the inventors were in possession of this invention as of the April 2020 filing date of the ’810 provisional. (Anticipated Testimony of Dr. Channick.)



387. Dr. Wertheim has taken the position that the '810 provisional application “directly communicates to the POSA that the method of treatment it describes will result in an improvement in exercise capacity.” (Anticipated Testimony of Dr. Wertheim.) Dr. Wertheim finds his purported support for this argument in paragraph [0009] of the '810 provisional application which states that the methods described will result in an “improvement in symptoms such as shortness of breath and fatigue.” (Anticipated Testimony of Dr. Wertheim.) Dr. Wertheim has further argued that “improvements in symptoms associated with exercise capacity are echoed in claims 9-11 of the '810 Provisional Application,” because they cover “reductions in fatigue and/or shortness of breath.” (Anticipated Testimony of Dr. Wertheim.) Dr. Wertheim also relies on Example 1 of the '810 provisional application, similarly arguing that a correlation between the clinical endpoints disclosed in Example 1 and the '327 patent's claimed “improvements in exercise capacity” demonstrate that a POSA would understand the '810 provisional application to cover improvements in exercise capacity in PH-ILD patients. (Anticipated Testimony of Dr. Wertheim.)

388. Importantly, Dr. Wertheim does not point to any actual results demonstrating any improvement in shortness of breath, 6MWD, or any other parameter supporting an improvement in exercise capacity. This failure is glaring given the position taken by the inventors, and advocated by Dr. Nathan, that the invention of the '327 patent was not conceived and completed until the results of the INCREASE study were actually obtained. (Anticipated Testimony of Dr. Nathan.) If the inventors and Dr. Nathan believe that they did not have an invention until results were disclosed, then there is no way a POSA looking at the '810 application would conclude that the inventors were in possession of a method of improving the exercise capacity of a PH-ILD patient. (Anticipated Testimony of Dr. Channick.)

389. Dr. Wertheim has relied on purported literature linking changes in FVC to changes in exercise capacity to support his position that because the '810 provisional application discloses statistically significant improvement in FVC, then improvement in 6MWD would also be statistically significant and this would in turn cover the full scope of claim 1 of the '327 patent. (Anticipated Testimony of Dr. Wertheim.) None of the literature cited by Dr. Wertheim supports his proposition that there is any correlation between FVC and exercise capacity in PH-ILD patients. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Dr. Ogenstad.) Further, none of the literature cited by Dr. Wertheim is related to treprostinil. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Dr. Ogenstad.) Moreover, the literature is also not based on patients diagnosed with PH-ILD, as required by the '327 patent claims, but instead to different ILD conditions. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Dr. Ogenstad.) These papers simply do not support the idea that there is a correlation between FVC and 6MWD in PH-ILD patients treated with inhaled treprostinil. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Dr. Ogenstad.) Thus, from a clinical perspective, the publications do not support Dr. Wertheim's opinion that a POSA would understand the '810 provisional application to disclose improvements in exercise capacity or any other claimed outcome. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Dr. Ogenstad.)

390. Claims 2–11 and 14–19 all depend from claim 1. ('327 patent at Claims 1-11, 14-19.) Because the '327 patent inventors were not in possession of the invention claimed in claim 1 as of the April 2020, they also cannot be in possession of the invention claimed in dependent claims 2-11 and 14-19. Further, claim 2 requires a “statistically significant” change in 6MWD, whereas claims 3 and 17-19 require varying degrees of demonstrated improvements in 6MWD such as an

increase of “10 m after 8 weeks, 12 weeks, or 16 weeks.” (*Id.* at Claims 2-3 and 17-19.) There is no data in the ’810 provisional to support these improvements in 6MWD and thus a POSA would conclude the inventors were not in possession of the invention claimed in these asserted dependent claims as of the April 2020 filing date of the ’810 provisional. (Anticipated Testimony of Dr. Channick.) The same is true for claims 4–5 directed to improvements in NT-proBNP, and claims 6–8, which require “statistically significant” reductions in exacerbations of interstitial lung disease and clinical worsening events. (*Id.* at Claims 4-8.) For the additional reasons below, none of the Asserted Claims has priority support in the ’810 Application.<sup>4</sup>

391. With respect to claim 2, Dr. Wertheim has argued that statistically significant improvements in percent predicted FVC and statistically significant reductions in acute exacerbations would lead a POSA to conclude that there would have been a statistically significant improvement in 6MWD as well even in the absence of data. (Anticipated Testimony of Dr. Wertheim.) However, the publications which Dr. Wertheim cites for this opinion do not establish a correlation between FVC and 6MWD in PH-ILD patients, let alone a correlation involving inhaled treprostinil resulting in a statistically significant improvement in the 6MWD test. (Anticipated Testimony of Dr. Channick.) Dr. Wertheim also does not provide any support for his opinion that a statistically significant result in a safety endpoint results in a statistically significant result in an efficacy endpoint. (Anticipated Testimony of Dr. Channick.) Nonetheless, if statistical significance in FVC proves statistical significance in 6MWD, without any 6MWD data, then a

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<sup>4</sup> Dr. Wertheim does not offer any priority date opinions for Asserted Claims 3-5, 12, 13, and 17-19 of the ’327 patent; and therefore does not dispute that Asserted Claims 3-5 12, 13, and 17-19 are not entitled to priority based on the filing of the ’810 provisional.

statistical significance improvement in 6MWD like that established in Agarwal 2015 and Faria-Urbina 2018 proves statistical significance in FVC. (Anticipated Testimony of Dr. Channick.)

392. Claim 6 depends from claim 1 and additionally requires that the administration of inhaled treprostinil “provide[] a statistically significant reduction of at least one exacerbations of the interstitial lung disease.” (’327 patent at Claim 6.) A POSA would not understand the inventors were in possession of claim 6. Dr. Wertheim and UTC have taken the position that a POSA would understand from the data reported in Example 1 and Figure 1 that administration of inhaled treprostinil resulted in a statistically significant reduction of ILD exacerbations versus placebo. (Anticipated Testimony of Dr. Wertheim.) However, while Section [0009] of the ’810 provisional discloses various symptoms including “shortness of breath, fatigue, weight loss, dry cough, chest pain, and lung hemorrhage[,]” there is no actual data presented and Section [0009] is simply an assumption that an improvement will result. (Anticipated Testimony of Dr. Channick; DTX0375, ’810 provisional at UTC\_PH-ILD\_069476 ([0009]).) These disclosures are concerned with exacerbations as a function of time and do not provide the statistically significant reduction of at least on exacerbation, as required by claim 6. (Anticipated Testimony of Dr. Channick.)

393. Dr. Wertheim has also argued that the ’810 provisional application discloses the INCREASE study results. (Anticipated Testimony of Dr. Wertheim.) It does not. Nor does Figure 1 of the ’810 provisional application communicate a statistically significant reduction in exacerbations. (Anticipated Testimony of Dr. Channick.) Figure 1 demonstrates “Time to Exacerbation” in the Inhaled Treprostinil and Placebo arms of the study. (Anticipated Testimony of Dr. Channick.) Section [0082] merely states that “time to exacerbation of underlying disease” was an exploratory endpoint and Dr. Wertheim has not explained how a measurement of time would convey to a POSA that the data demonstrated a statistically significant reduction of at least

one exacerbation of the interstitial lung disease. (Anticipated Testimony of Dr. Channick.) Thus, neither of these disclosures conveys what claim 6 of the '327 patent requires and are instead concerned with exacerbations as a function of time. (Anticipated Testimony of Dr. Channick.)

394. Claim 7 of the '327 patent requires a statistically significant “reduction of clinical worsening events due to interstitial lung disease.” ('327 patent at Claim 7.) Dr. Wertheim has admitted that Example 1 of the '810 provisional application does not directly report on the incidence of clinical worsening in the active and placebo arms of the study. (Anticipated Testimony of Dr. Wertheim.) Dr. Wertheim has also described clinical worsening as a number of serious adverse consequences including hospitalization, significant reductions in exercise capacity, loss of lung function, and even death. (Anticipated Testimony of Dr. Wertheim.) A POSA would not understand that a statistically significant increase in percent predicted FVC would demonstrate that a patient would also experience a statistically significant reduction in clinical worsening. (Anticipated Testimony of Dr. Channick.) This is further supported by inventor testimony that they did not possess the invention without obtaining actual data from INCREASE.

395. Claim 8 of the '327 patent depends from claim 7 and additionally requires that the “clinical worsening events” include either “hospitalization for cardiopulmonary indication” or decrease in 6MWD “by more than 15% compared a baseline[.]” ('327 patent at Claim 8.) Dr. Wertheim and UTC have taken the position that a POSA reading the data reported in Example 1 of the '810 provisional application would understand that the patients in the study experienced a statistically significant reduction in clinical worsening events and would further understand that the reduction in clinical worsening events would include at least one of: (i) hospitalization for cardiopulmonary indication and (ii) a decrease in 6MWD by more than 10% compared to baseline.

(Anticipated Testimony of Dr. Wertheim.) This position assumes that a POSA would understand acute exacerbations of underlying lung disease typically result in hospitalizations for PH-ILD patients and further assumes that a POSA would understand from Example 1 that the reported statistically significant improvement in percent predicted FVC across the patient population would be accompanied by a corresponding improvement in exercise capacity, e.g., as reflected by increased 6MWD. However, the '810 provisional does not disclose any actual data with respect to clinical worsening events and there is no basis to extrapolate an already tenuous to non-existent correlation between FVC and 6MWD to clinical worsening. (Anticipated Testimony of Dr. Channick.)

396. Dr. Wertheim has argued that there is a correlation or causal relationship between the FVC and exacerbation data reported in Example 1 and the particular clinical worsening events described in claim 8 of the '327 patent that would lead a POSA to conclude that the inventors were in possession of the method described in claim 8 of the '327 patent. (Anticipated Testimony of Dr. Wertheim.) Dr. Wertheim has cited three publications to support his proposition that a POSA would understand that acute exacerbations of underlying lung disease typically result in hospitalizations for PH-ILD patients, yet none of these publications report results in the PH-ILD patient population, let alone discuss any purported correlation or alleged causal relationship between FVC and “hospitalization for cardiopulmonary indication” or decrease in 6MWD “by more than 15% compared a baseline.” (Anticipated Testimony of Dr. Channick.)

397. Claim 9 of the '327 patent depends from claim 1 and further requires that administration of treprostinil result in “statistically significant improve[ment] of forced vital capacity (FVC) in the patient after 8 weeks, 12[] weeks, or 16 weeks[.]” ('327 patent at Claim 9.) Claim 9 is directed to both absolute and percent predicted FVC. (Anticipated Testimony of Dr.

Channick.) The statistically significant result in FVC is required for the claimed “PH-ILD” patient population and statistically significant results were not obtained for the PH-ILD ITT population, but only sub-populations. (Anticipated Testimony of Dr. Channick.) Thus, the data in Example 1 would not convey to a POSA that the inventors were in possession of the invention of the full scope of claim 9. (Anticipated Testimony of Dr. Channick.) While Dr. Wertheim has attempted to sidestep this requirement by aggregating data from Tables 1-3 and concluding that based on the data reported in Example 1 of the ’810 provisional application, a POSA would understand that, on average, all patients showed a statistically significant improvement in percent predicted FVC as compared to placebo at both the 8 week and 16 week time points. (Anticipated Testimony of Dr. Wertheim.) However, this is not what Example 1 shows as it is clear that the ITT population, which is all of the patients, did not achieve a statistically significant result. (Anticipated Testimony of Dr. Channick.)

398. Claim 10 of the ’327 patent depends from claim 9 and additionally requires that the administration of treprostinil to the PH-ILD patient improve the patient’s FVC “by at least 20 mL after 8 weeks, 12 weeks, or 16 weeks of the administering.” (’327 patent at Claim 10.) Claim 10 depends from claim 9, which would indicate to a POSA that the improvement in FVC disclosed in claim 10 must be both statistically significant and “at least 20 mL after 8 weeks, 12 weeks, or 16 weeks of the administering.” (Anticipated Testimony of Dr. Channick.) Dr. Wertheim’s opinion that a POSA would understand that claim 10 of the ’327 patent could be satisfied if the improvement in the percent predicted FVC was statistically significant but the improvement in absolute FVC was not, is at odds with claim 10 which recites “at least 20 mL.” (Anticipated Testimony of Dr. Wertheim; ’327 patent at Claim 10.) 20 mL is an absolute FVC measurement, not a percent predicted measurement.

399. Claim 11 depends from claim 1 and additionally requires that the administration of inhaled treprostinil to the PH-ILD patient be “performed by a pulsed inhalation device.” (’327 patent at Claim 11.) A POSA would not conclude the inventors to have been in possession of claim 1 based on the disclosures of the ’810 provisional and would therefore not conclude that the inventors were in possession of the invention of claim 11. (Anticipated Testimony of Dr. Channick.)

400. Claim 14 depends from claim 11 and additionally requires that the “pulsed inhalation device” used to administer the inhaled treprostinil be “a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.” (’327 patent at Claim 14.) A POSA would not conclude the inventors to have been in possession of claim 1 based on the disclosures of the ’810 provisional and as claim 14 depends from claim 11, which depends from claim 1, a POSA would therefore not conclude that the inventors were in possession of the invention of claim 14. (Anticipated Testimony of Dr. Channick.)

401. Dr. Wertheim takes the position that paragraph [0060] of the ’810 provisional provides a real-world example of a dry powder formulation of treprostinil that is delivered by a breath-powered dry powder inhaler. (Anticipated Testimony of Dr. Wertheim.) However, neither the ’810 provisional application, nor the publications cited in paragraph [0060], contain real-world examples of the invention disclosed in claim 14 of the ’327 patent. (Anticipated Testimony of Dr. Channick.) paragraph [0060] of the ’810 provisional describes inhaled compositions which “may include any of those described in U.S. Patent No. 9,339,507 (including the commercial product Tyvaso® (treprostinil) Inhalation Solution), PCT/US2017/031301 and PCT/US2013/072647. (DTX0375, ’810 provisional at UTC\_PH-ILD\_069490 ([0060])). U.S. Patent No. 9,339,507 (“the ’507 patent”) discloses a “kit for treating pulmonary hypertension[,]” not a method for improving



exercise capacity. (DT0097, U.S. Patent No. 9,339,507 (LIQ\_PH-ILD\_00101803) at Claim 1.) While said kit comprises a formulation, such formulation, Tyvaso, is an “inhaled solution,” distinct from a “real-world example” of a dry powder inhaler comprising a dry powder comprising treprostinil. (Anticipated Testimony of Dr. Channick.) WO2017/192993 (publication of PCT/US2017/031301), which is Liquidia’s application, discloses a dry powder inhalation treatment for pulmonary arterial hypertension. (DTX0674, WO2017/192993 (publication of PCT/US2017/031301).) To the extent Dr. Wertheim relies on Liquidia’s application, it only establishes that Liquidia, not UTC, was first to disclose the actual use of a DPI formulation and device. WO2014/085813 (publication of PCT/US2013/072647), while mentioning dry powder inhalers, is directed to liposomal formulations. (DTX0673, WO2014/085813 (publication of PCT/US2013/072647).)

402. Claim 15 of the ’327 patent depends from claim 1 and additionally requires that the effective amount of treprostinil delivered to the PH-ILD patient in a single administration event be from 15 µg to 100 µg. (’327 patent at Claim 15.) A POSA would not conclude the inventors were in possession of the invention of claim 1 based on the disclosures of the ’810 provisional application. (Anticipated Testimony of Dr. Channick.) As claim 15 depends from claim 1, a POSA would not conclude that the inventors were in possession of the invention of claim 15. (Anticipated Testimony of Dr. Channick.)

403. Claim 16 of the ’327 patent depends from claim 15 and additionally requires that the administration of treprostinil in a single inhalation administration event “does not exceed 15 breaths by the patient. (’327 patent at Claim 16.) A POSA would not conclude the inventors were in possession of the invention of claim 1 based on the disclosures of the ’810 provisional application. (Anticipated Testimony of Dr. Channick.) As claim 16 depends from claim 15, which

depends from claim 1, a POSA would not conclude that the inventors were in possession of the invention of claim 16. (Anticipated Testimony of Dr. Channick.)

404. A POSA would thus not understand the disclosures and claims of Provisional Application No. 63/011,810 to describe and enable each and every limitation of every Asserted Claim of the '327 patent in light of the POSA's knowledge and the available prior art as of April 17, 2020. (Anticipated Testimony of Dr. Channick.)

### **VIII. ANTICIPATION**

#### **A. Claims 1-11 and 15-19 of the '327 Patent Are Anticipated by Prior Use**

405. Using inhaled treprostinil to treat PH-ILD patients was in public use and ready for patenting before April 17, 2020, the effective filing date of the '327 patent.<sup>5</sup> As discussed in Section V.B, physicians began off-label prescribing Tyvaso to treat PH-ILD as early as 2009 when inhaled treprostinil became commercially available to treat PAH. These physicians followed the same PAH dosing regimen described in the 2009 Tyvaso label to improve exercise capacity in PH-ILD patients. UTC documented at least four instances of this off-label use in its FAERS Public Dashboard between 2014 and 2018. (*See id.*) And top-ranking executives at UTC, including the CEO, Dr. Rothblatt, and Executive Vice President of Global Regulatory Affairs, Mr. Bunce, knew about this off-label use before the '327 patent's effective filing date. (*See id.*) Insurance payors also knew about this off-label use, as several had approved the sale of Tyvaso for this purpose. (*See id.*) Based on this evidence, the subject matter claimed in the '327 patent was available to the public, actually used and ready for patenting, due to the claimed subject matter being reduced to practice.

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<sup>5</sup> Although we disagree that the '327 patent should receive a priority date of April 17, 2020 (*see* Section VII above), for Section VIII, we presume that the '327 patent is entitled to the April 17, 2020 priority date.

**1. Claim 1 of the '327 Patent is Invalid by The Public Use of Tyvaso®**

**a. Claim 1[a]: “A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising”**

406. Claim 1[a] was in public use and ready for patenting before the '327 patent's effective filing date, April 17, 2020. At least as early as 2009, Tyvaso®, along with the 2009 Tyvaso® Label, was publicly available in the United States. (*See* DTX0357, 2009 Tyvaso® Label, UTC\_PH-ILD\_010692.) As discussed in Section V.B, physicians were publicly practicing Claim 1[a] as early as 2009 using Tyvaso. This public use involved physicians off-label prescribing Tyvaso to treat PH-ILD patients in the ordinary course of their practice and physicians giving presentations and publishing peer-reviewed journal articles on how they improved PH-ILD patients' exercise capacity by administering inhaled treprostinil. (*See id.*)

407. As discussed in Section V.B, Drs. Channick, Hill, Tapson, Saggar, and Parikh provide testimony on their real-world use of Tyvaso, using the recommended Tyvaso dosing, to improve the exercise capacity of PH-ILD patients. This evidence alone provides the public use and accessibility of claim 1[a].

408. Not only did physicians actually use Tyvaso to improve the exercise capacity in PH-ILD patients, they disclosed such use in publications. As discussed in Sections V.C.3 and V.C.6 above, in 2015 and 2018 Dr. Waxman published two retrospective studies that showed PH-ILD patients experiencing a statistically significant improvement in 6MWD following administration of inhaled treprostinil (Agarwal 2015 and Faria-Urbina 2018, respectively). And as discussed in Section V.C.4 above, Dr. Parikh published an article in 2016 (Parikh 2016), which concluded that Tyvaso has a favorable safety and tolerability profile in WHO Group 3 patients, including PH-ILD patients.

409. UTC was also internally aware of the prior use of treprostinil, including inhaled treprostinil. Several emails produced by UTC during this litigation also demonstrate that claim 1[a] was in public use by Drs. Rajeev Saggar, Rajan Saggar, and Victor Tapson prior to the '327 patent's effective filing date. Dr. Rajeev Saggar, for instance, invited Dr. Martine Rothblatt to "collaborate" in June 2010, noting "there is no doubt that UT's products are the key to succeed in treating ILD-PH." (DTX0676, SAGGAR\_PH-ILD\_000022 at -023.) A day later, Dr. Rothblatt sent an email to Dr. Rajeev Saggar asking to meet his team, to which Dr. Rajeev Saggar replied, specifically noting that they would "likely start enroll[ment] in pulmonary fibrosis/PAH study in the next month or so." (*Id.* at -022.) On June 16, 2010, Dr. Rothblatt replied to this June 13, 2010, email for Dr. Rajeev Saggar, in an email with a subject line reading "Tre for IPF/ILD" stating "I have no doubt we will pursue with you tre for ILD/IPF." (*Id.*) Six days later, in a separate email string dated June 19, 2010, Dr. Rajeev Saggar contacted Griselda Maldonado and Robert Daye asking that a meeting room be booked for a meeting with Martine Rothblatt, listing the discussion as "ILD-PAH and parenteral prostacyclin," and listing the following invitees who were subsequently forwarded the June 19 email: Rajeev Saggar, Rajan Saggar, Joseph Lynch, Steve Dubinett, and John Belperio. (DTX0675, SAGGAR\_PH-ILD\_000001.)

410. Dr. Rothblatt additionally emailed Roger Jeffs on November 25, 2015, noting that Dr. Victor Tapson had stated there was "nothing else for IPF (and also ILD) as good as Tyvaso[.]" (DTX0610, UTC\_WAT00628950 at -951.) Dr. Rothblatt responded that the "Saggar brothers [have the] same POV." (*Id.*)

411. As discussed more fulsomely below in Section VIII.B, claim 1[a] was also commercially exploited by off-label prescriptions of Tyvaso to PH-ILD patients, thereby further establishing that it was in public use prior to the '327 patent's effective filing date.

412. Claim 1[a] was also ready for patenting. As discussed, physicians were actually able to increase PH-ILD patients' exercise capacity using the 2009 Tyvaso label's dosing regimen. (*See* Section V.B; *see also* Section VIII.A.2.) Thus, physicians' actual use of Tyvaso, using the directed dosing regime, led to an improvement in exercise capacity in PH-ILD patients, reducing this limitation to practice and thus making it ready for patenting.

**2. Claim 1[b]-[d]: “administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.”**

413. Claim limitation 1[b]-[d] of the '327 patent was in public use and ready for patenting more than one year before the patent's priority date. As discussed in Section V.B, physicians used Tyvaso, and the Tyvaso label dosing recommendations to improve the exercise capacity in PH-ILD patients. As described in Section V.B, the dosing regimen disclosed in the 2009 Tyvaso label meets the limitations of claim 1[b]-[d]. Indeed, as discussed in Section V.A.2, the dosing in the 2009 Tyvaso label is the same as the dosing in the 2021 Tyvaso label, which contains both the PAH and PH-ILD indications. (DTX0360, 2021 Tyvaso® Label, UTC\_PH-ILD\_010744.) Thus, claim 1[b]-[d] was in public use. As discussed more fulsomely below in Section VIII.B, claim 1[b] was also commercially exploited by off-label prescriptions of Tyvaso to PH-ILD patients, thereby further establishing that it was in public use prior to the '327 patent's effective filing date.

414. Claim 1[b]-[d] was also ready for patenting. As discussed, physicians were able to increase PH-ILD patients' exercise capacity using the 2009 Tyvaso label's dosing regimen. (*See* Section V.B; *see also* Section VIII.A.2.) Thus, physicians' actual use of Tyvaso, using the directed dosing regime, led to an improvement in exercise capacity in PH-ILD patients, reducing this

limitation to practice and thus making it ready for patenting. Accordingly, the totality of claim 1 is invalid for prior public use.

**3. Dependent Claims 2-11 and 15-19 are Invalid by The Public Use of Tyvaso®**

415. Dependent claims 2-11 and 15-19 were in public use and ready for patenting before the '327 patent's priority date. For the same reasons discussed above in claims 1[a] and 1[b]-[d], claims 2-11 and 15-19 were in public use vis-à-vis physicians' public use of Tyvaso according to the dosing regimen disclosed by the 2009 Tyvaso label. (*See* Sections VIII.A.1 and VIII.A.2.) As discussed more fulsomely below, because physicians followed the dosing regimen disclosed in the 2009 Tyvaso label when treating PH-ILD patients (*see* Sections VIII.A.1 and VIII.A.2), dependent claims 2-11 and 15-19 were also ready for patenting.

**a. Claim 2: "The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering."**

416. As discussed above with respect to claim 1, physicians using Tyvaso in PH-ILD patients actually improved the exercise capacity in PH-ILD patients. This real-world use was disclosed in publications written by these physicians, including Dr. Waxman who is the senior author on Faria-Urbina 2018. As disclosed in Section V.C.6, Faria-Urbina discloses not only an improvement in the 6MWD test, but PH-ILD patients with CPFE experienced a statistically significant improvement in this outcome. As such, claim 2, which requires a statistically significant increase in the 6MWD test after weeks 8, 12, or 16, was in public use.

417. The subject matter of claim 2 was also ready for patenting based on the actual results obtained by the physicians' prior use of Tyvaso. The results obtained by physicians, and disclosed in publications, evidence actual reduction to practice, rendering the subject matter of claim 2 ready for patenting. For these reasons, claim 2 is invalid for prior public use.

418. The 2009 Tyvaso Label discloses the TRIUMPH I study, which was used to obtain approval for Tyvaso to treat Group I PAH patients. (DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010697.) As shown in the excerpt below, the TRIUMPH I study evaluated the six-minute walk distance of patients after 12 weeks of treatment with Tyvaso and patients had a median increase of 20 meters in six-minute walk distance at Week 12 ( $p < 0.001$ ).

#### 14 CLINICAL STUDIES

TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable subjects with pulmonary arterial hypertension (WHO Group I), nearly all with NYHA Class III symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in four daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/familial (56%), secondary to collagen vascular disease (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ( $p < 0.001$ ). The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

(DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010703 (highlighting added).)

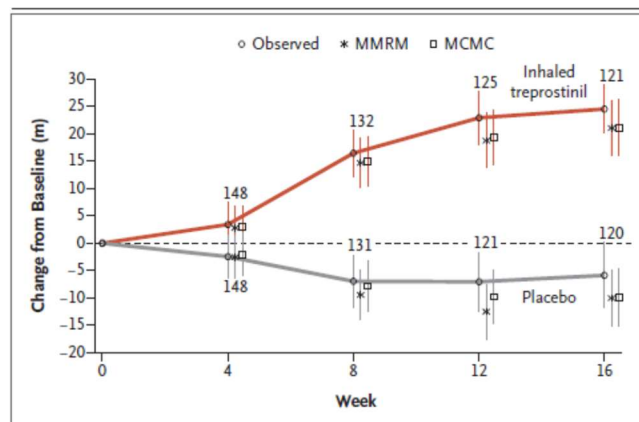
419. And using the same dosing regimen, the INCREASE study demonstrated results including a statistically significant increase of 31.12 meters in six-minute walk distance over 16 weeks of treatment compared to the placebo group.



#### PRIMARY END POINT

Mean within-group changes in the 6-minute walk distance are shown in Figure 2. Mixed-model repeated-measures analysis showed that the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in peak 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39;  $P < 0.001$ ) (Table 2 and Fig. S1). Similar effects were observed across subgroups, including subgroups defined by disease cause and severity (as measured by baseline 6-minute walk distance), baseline hemodynamics, and dose group (Fig. S2). In addition, the between-group difference in the change from baseline in peak 6-minute walk distance at week 16 was significant when analyzed with multiple imputation according to the Markov chain Monte Carlo method (30.97 m; 95% CI, 16.53 to 45.41;  $P < 0.001$ ) (Fig. S3).

(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010793 (highlighting added).)



**Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.**

Shown are mean ( $\pm$ SE) changes from baseline (dashed line) in peak 6-minute walk distance over the 16-week trial period. The data shown are for patients with available data (observed) as well as for the results of two analysis methods used to account for missing data. The values shown at each data point indicate the number of patients assessed at that time point. The primary analysis used mixed-model repeat-measurement (MMRM) methods, with the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed with the use of a multiple imputation approach with a multivariate normal imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation model included treatment group, all scheduled visits, patient's sex, and patient's age at randomization. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010796 (Fig. 2).)



420. Thus, based on the disclosure in the 2009 Tyvaso Label and the INCREASE study, the physicians' use of Tyvaso to treat PH-ILD patients would necessarily and inevitably provide a statistically significant increase in 6-minute walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering, and disclose claim 2. (Anticipated testimony of Dr. Hill.)

- b. **Claim 3: "The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering."**

421. For the same reasons as claim 2, claim 3 is invalid for prior public use.

- c. **Claim 4: "The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering."**

422. The subject matter of claim 4 is invalid for prior public use. The dosing regimen of the 2009 Tyvaso Label is the same as that used in the INCREASE study. For example, comparing the 2009 Tyvaso Label and the INCREASE study description posted on ClinicalTrials.gov on February 10, 2017 ("2017 INCREASE Study Description"):

- DOSAGE AND ADMINISTRATION-----
- Use only with the Tyvaso Inhalation System. (2.1)
  - Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. (2.1)
  - Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours. (2.1)
  - Initial dosage: 3 breaths [18 mcg] per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. (2.1)
  - Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated. (2.1)
  - Titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated. (2.1)

(DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010693 (highlighting added).)

Arms and Interventions	
Arms	Assigned Interventions
Placebo Comparator: Placebo  Matching placebo inhaled using an ultrasonic nebulizer four times daily	Drug: Placebo  <ul style="list-style-type: none"> <li>Placebo administered four times daily</li> </ul>
Active Comparator: Active Inhaled Treprostinil  Active Treprostinil for inhalation solution (0.6 mg/mL) delivered via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath. Inhaled four times daily and titrated up to a maximum of 12 breaths four times daily	Drug: Inhaled Treprostinil  <ul style="list-style-type: none"> <li>Inhaled treprostinil (6 mcg/breath) administered four times daily</li> <li>Other Names:                             <ul style="list-style-type: none"> <li>Tyvaso</li> </ul> </li> </ul>

(DTX0008, 2017 INCREASE Study Description at LIQ\_PH-ILD\_00000194 (highlighting added).)

423. Both the 2009 Tyvaso label and the 2017 INCREASE Study Description show a dosing regimen of three breaths of Tyvaso in a single treatment session up to four times daily, where a single breath of Tyvaso delivers approximately 6 micrograms of treprostinil. And using the same dosing regimen, the INCREASE study showed a statistically significant reduction in blood NT-proBNP levels after 16 weeks of administering Tyvaso:

#### RESULTS

A total of 326 patients underwent randomization, with 163 assigned to inhaled treprostinil and 163 to placebo. Baseline characteristics were similar in the two groups. At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39;  $P<0.001$ ). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72;  $P<0.001$ ). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92;  $P=0.04$  by the log-rank test). The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010790.)

424. Thus, based on the disclosure in the INCREASE study, the physicians' use of Tyvaso to treat PH-ILD patients would necessarily and inevitably provide a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16

weeks of the administering and disclose claim 4. (Anticipated testimony of Dr. Hill.) For this reason, the subject matter of claim 4 was in public use and ready for patenting, rendering claim 4 invalid for prior public use.

**d. Claim 5: “The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.”**

425. The subject matter of claim 5 is invalid for prior public use. As explained above for claim 4, the 2009 Tyvaso Label and the INCREASE study use the same dosing regimen. The INCREASE study results include a reduction in plasma NT-proBNP concentration of at least 200 pg/ml after 16 weeks of administering Tyvaso, as shown in the excerpts below.

Table 2. Summary of Primary and Secondary End Points.*				
End Point	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	Treatment Effect (95% CI)	P Value
<b>Primary end point</b>				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	-10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
<b>Secondary end points§</b>				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	-396.35±1904.90	1453.95±7296.20		
Median — pg/ml	-22.65	20.65		
Range — pg/ml	-11,433.0 to 5373.1	-5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	-12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	-12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010797 (Table 2) (highlighting added).)

426. Thus, based on the disclosure in the INCREASE study, the physicians' use of Tyvaso to treat PH-ILD patients would necessarily and inevitably reduce a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering and discloses claim 5. (Anticipated testimony of Dr. Hill.) For this reason, the subject matter of claim 5 was in public use and ready for patenting, rendering claim 5 invalid for prior public use.

**e. Claim 6: "The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease."**

427. The subject matter of claim 6 is invalid for prior public use. As explained above for claim 4, the 2009 Tyvaso Label and the INCREASE study use the same dosing regimen. The INCREASE study discloses significantly fewer patients in the treprostinil group experiencing exacerbations of underlying lung disease when compared to the patients in the placebo group:

Significantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (43 [26.4%] vs. 63 [38.7%];  $P=0.02$  by Fisher's exact test). Fewer patients in the treprostinil group than in the placebo group had a first occurrence of clinical worsening that involved hospitalization for a cardiopulmonary indication (18 [11.0%] vs. 24 [14.7%];  $P=0.41$ ). Inhaled treprostinil had no deleterious effect on any pulmonary function test variable during the trial (Table S6). There were no significant treatment-related changes in pulse oximetry or supplemental oxygen use in either group over the trial period (Tables S7 and S8).

(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010796 (highlighting added).)

428. Also, Dr. Waxman characterized exacerbations of interstitial lung disease as "worsening oxygenation, worsening shortness of breath[.]" both of which are tied to respiratory deterioration. (See Waxman Depo. Tr. at 115:15-116:2.) Because the INCREASE study discloses a statistically significant improvement in six-minute walk distance, this would reflect a statistically

significant reduction in respiratory deterioration and consequently a statistically significant reduction in exacerbations of lung disease.

429. Thus, based on the disclosure in the INCREASE study, the physicians' use of Tyvaso to treat PH-ILD patients would necessarily and inevitably provide a statistically significant reduction of at least one exacerbations of the interstitial lung disease and discloses claim 6. (Anticipated testimony of Dr. Hill.) For this reason, the subject matter of claim 6 was in public use and ready for patenting, rendering claim 6 invalid for prior public use.

**f. Claim 7: "The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease."**

430. The subject matter of claim 7 is invalid for prior public use. As explained above for claim 4, the 2009 Tyvaso Label and the INCREASE study use the same dosing regimen. The INCREASE study discloses significantly fewer patients in the treatment group experiencing clinical worsening when compared to the patients in the placebo group:

**RESULTS**

A total of 326 patients underwent randomization, with 163 assigned to inhaled treprostinil and 163 to placebo. Baseline characteristics were similar in the two groups. At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39;  $P < 0.001$ ). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72;  $P < 0.001$ ). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92;  $P = 0.04$  by the log-rank test). The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010790 (highlighting added).)



placebo, as assessed by the least-squares mean for the log-transformed ratio to the baseline level at week 16 (treatment ratio, 0.58; 95% CI, 0.47 to 0.72;  $P < 0.001$ ) (Fig. S4). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92;  $P = 0.04$  by the log-rank test) (Fig. S5). The least-squares mean change from baseline to week 12 in peak 6-minute walk distance was 31.29 m greater in the treprostinil group than in the placebo group ( $P < 0.001$ ), and the change

(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010794 (highlighting added).)

431. Thus, based on the disclosure in the INCREASE study, the physicians' use of Tyvaso to treat PH-ILD patients would necessarily and inevitably provide a statistically significant reduction of clinical worsening events due to the interstitial lung disease and discloses claim 7. (Anticipated testimony of Dr. Hill.) For this reason, the subject matter of claim 7 was in public use and ready for patenting, rendering claim 7 invalid for prior public use.

- g. Claim 8: "The method of claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering."**

432. For the same reason as claim 7, as well as claim 2, the subject matter of claim 8 is invalid for prior public use.

- h. Claim 9: "The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering."**

433. The subject matter of claim 9 is invalid for prior public use. As explained above for claim 4, the 2009 Tyvaso Label and the INCREASE study use the same dosing regimen. The INCREASE Study reports a statistically significant improvement of FVC % predicted after 8 weeks and 16 weeks of administering treprostinil to patients with PH-ILD:

**Table S6. Analysis of Lung Function Test Parameters Using Mixed Model Repeated Measurement.**

Variable Visit Treatment	N	LS Mean	Contrast: Inhaled treprostinil - Placebo Estimated Difference (95% CI)	P-value
<b>FVC (mL)</b>				
Week 8				
Inhaled treprostinil	142	5.49	28.47	
Placebo	141	-22.98	(-30.81, 87.74)	0.35
Week 16				
Inhaled treprostinil	130	9.77	44.40	
Placebo	126	-34.63	(-25.25, 114.05)	0.21
<b>FVC (% predicted)</b>				
Week 8				
Inhaled treprostinil	142	0.77	1.79	
Placebo	141	-1.02	(0.37, 3.21)	0.01
Week 16				
Inhaled treprostinil	130	1.07	1.80	
Placebo	126	-0.72	(0.20, 3.39)	0.03
<b>FEV<sub>1</sub> (mL)</b>				
Week 8				
Inhaled treprostinil	142	-21.34	-8.95	
Placebo	141	-12.39	(-57.16, 39.26)	0.72
Week 16				
Inhaled treprostinil	130	-32.18	-2.56	
Placebo	126	-29.62	(-57.67, 52.55)	0.93
<b>FEV<sub>1</sub> (% predicted)</b>				
Week 8				
Inhaled treprostinil	142	-0.18	0.57	
Placebo	141	-0.75	(-0.83, 1.96)	0.43
Week 16				
Inhaled treprostinil	130	-0.24	0.38	
Placebo	126	-0.62	(-1.25, 2.01)	0.65
<b>TLC (mL)</b>				
Week 8				
Inhaled treprostinil	135	-38.75	-16.23	
Placebo	136	-22.51	(-141.9, 109.41)	0.80
Week 16				
Inhaled treprostinil	127	45.43	17.37	
Placebo	116	28.06	(-158.9, 193.61)	0.85
<b>TLC (% predicted)</b>				
Week 8				
Inhaled treprostinil	135	-0.05	0.28	
Placebo	136	-0.32	(-1.49, 2.05)	0.76
Week 16				
Inhaled treprostinil	127	2.52	1.49	
Placebo	116	1.03	(-1.57, 4.54)	0.34

(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010825 (highlighting added).)

434. Thus, based on the disclosure in the INCREASE study, the physicians' use of Tyvaso to treat PH-ILD patients would necessarily and inevitably provide a statistically significant improvement of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering and discloses claim 9. (Anticipated testimony of Dr. Hill.)

- i. **Claim 10: “The method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.”**

435. The subject matter of claim 10 is invalid for prior public use. As explained above for claim 4, the 2009 Tyvaso Label and the INCREASE study use the same dosing regimen. The INCREASE Study showed a 28.47 ml estimated difference in FVC between the treatment group and placebo group at week 8 and a 44.40 ml estimated difference at week 16:

**Table S6. Analysis of Lung Function Test Parameters Using Mixed Model Repeated Measurement.**

Variable Visit	Treatment	N	LS Mean	Contrast: Inhaled treprostinil - Placebo Estimated Difference (95% CI)	P-value
<b>FVC (mL)</b>					
<b>Week 8</b>					
Inhaled treprostinil		142	5.49	28.47	0.35
Placebo		141	-22.98	(-30.81, 87.74)	
<b>Week 16</b>					
Inhaled treprostinil		130	9.77	44.40	0.21
Placebo		126	-34.63	(-25.25, 114.05)	
<b>FVC (% predicted)</b>					
<b>Week 8</b>					
Inhaled treprostinil		142	0.77	1.79	0.01
Placebo		141	-1.02	(0.37, 3.21)	
<b>Week 16</b>					
Inhaled treprostinil		130	1.07	1.80	0.03
Placebo		126	-0.72	(0.20, 3.39)	
<b>FEV<sub>1</sub> (mL)</b>					
<b>Week 8</b>					
Inhaled treprostinil		142	-21.34	-8.95	0.72
Placebo		141	-12.39	(-57.16, 39.26)	
<b>Week 16</b>					
Inhaled treprostinil		130	-32.18	-2.56	0.93
Placebo		126	-29.62	(-57.67, 52.55)	
<b>FEV<sub>1</sub> (% predicted)</b>					
<b>Week 8</b>					
Inhaled treprostinil		142	-0.18	0.57	0.43
Placebo		141	-0.75	(-0.83, 1.96)	
<b>Week 16</b>					
Inhaled treprostinil		130	-0.24	0.38	0.65
Placebo		126	-0.62	(-1.25, 2.01)	
<b>TLC (mL)</b>					
<b>Week 8</b>					
Inhaled treprostinil		135	-38.75	-16.23	0.80
Placebo		136	-22.51	(-141.9, 109.41)	
<b>Week 16</b>					
Inhaled treprostinil		127	45.43	17.37	0.85
Placebo		116	28.06	(-158.9, 193.61)	
<b>TLC (% predicted)</b>					
<b>Week 8</b>					
Inhaled treprostinil		135	-0.05	0.28	0.76
Placebo		136	-0.32	(-1.49, 2.05)	
<b>Week 16</b>					
Inhaled treprostinil		127	2.52	1.49	0.34
Placebo		116	1.03	(-1.57, 4.54)	



(DTX0363, Waxman 2021 at UTC\_PH-ILD\_010825 (highlighting added).)

436. Thus, based on the disclosure in the INCREASE study, the physicians' use of Tyvaso to treat PH-ILD patients would necessarily and inevitably improve the FVC in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering and discloses claim 10. (Anticipated testimony of Dr. Hill.)

**j. Claim 11: "The method of claim 1, wherein said administering is performed by a pulsed inhalation device."**

437. As discussed in Section V.B, physicians used Tyvaso to treat PH-ILD patients and improve their exercise capacity. Tyvaso uses a pulsed inhalation device to administer treprostinil via inhalation. *See* Section V.A.2. Accordingly, the subject matter of claim 11 is invalid based on physicians' prior public use of Tyvaso to improve the exercise capacity of PH-ILD patients.

**k. Claim 15: "The method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg."**

438. As discussed in Section V.B, physicians used Tyvaso, in accordance with the 2009 Tyvaso label, to treat PH-ILD patients and improve their exercise capacity. The 2009 Tyvaso label discloses administering inhaled treprostinil in a single administration event from 15 µg to 100 µg. *See* Section V.A.2. Accordingly, the subject matter of claim 15 is invalid based on physicians' prior public use of Tyvaso to improve the exercise capacity of PH-ILD patients.

**l. Claim 16: "The method of claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient"**

439. As discussed in Section V.B, physicians used Tyvaso, in accordance with the 2009 Tyvaso label, to treat PH-ILD patients and improve their exercise capacity. The 2009 Tyvaso label discloses administering inhaled treprostinil that does not exceed 15 breaths. *See* Section V.A.2.

Accordingly, the subject matter of claim 16 is invalid based on physicians' prior public use of Tyvaso to improve the exercise capacity of PH-ILD patients.

- m. Claim 17: "The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering."**

440. For the same reason as claims 2 and 3, the subject matter of claim 17 is invalid based on physicians' prior public use of Tyvaso to improve the exercise capacity of PH-ILD patients.

- n. Claim 18: "The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering."**

441. For the same reason as claims 2 and 3, the subject matter of claim 18 is invalid based on physicians' prior public use of Tyvaso to improve the exercise capacity of PH-ILD patients.

- o. Claim 19: "The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering."**

442. For the same reason as claims 2 and 3, the subject matter of claim 19 is invalid based on physicians' prior public use of Tyvaso to improve the exercise capacity of PH-ILD patients.

**B. Claims 1-11 and 15-19 of the '327 Patent Are Anticipated by Prior Sale**

443. Inhaled treprostinil was on-sale to improve the exercise capacity of PH-ILD patients before the effective filing date of the '327 patent (which was April 17, 2020). As discussed above in Section V.B, physicians were off-label prescribing Tyvaso to treat PH-ILD as early as 2009. These physicians obtained insurance coverage for these off-label prescriptions by describing their patients as having PH "out of proportion" with ILD. (See Section V.B.) UTC was aware of

the sales of Tyvaso to off-label treat PH-ILD and documented such sales within FDA's FAERS Public Dashboard as early as 2014. (*See* Section V.B.)

444. As already discussed above in the context of prior use (*see* Section VIII.A), the subject matter disclosed in claims 1-11 and 15-19 were ready for patenting before the priority date of the '327 patent. For the reasons discussed herein, the subject matter of claims 1-11 and 15-19 were subject to a commercial offer for sale

**1. Claims 1-11 and 15-10 of the '327 Patent are Invalid by UTC's Prior Sale of Tyvaso®**

445. As discussed above, physicians were using Tyvaso to treat PH-ILD patients. Before April 17, 2020, and as least as early as 2009, Tyvaso® was subject to a commercial offer for sale to improve exercise capacity in PH-ILD patients. As discussed above in Section V.B, physicians obtained insurance coverage for off-label prescriptions of Tyvaso to treat PH-ILD. Dr. Tapson described how he would prescribe Tyvaso such that it would get reimbursed by payors:

Q Back when you were at Duke, you had mentioned that the treprostinil products were expensive. How when you were prescribing Tyvaso® for PH-ILD patients, how did you prescribe it such that it would be reimbursed to the patient?

THE WITNESS: Well, all the PH products are expensive. But fortunately I had a good clinic nurse that would handle all that. But if someone had pulmonary hypertension and ILD and had very severe pulmonary hypertension, this could easily be considered, and what we felt was PH in the setting of ILD or it was hard to distinguish from ILD-causing PH or being coincidence. So we didn't really have difficulty. We didn't do it that often because we didn't have, you know, a lot of data but when we did it and felt we needed to, we could get it reimbursed.

(Tapson Depo. Tr. at 63:23-64:15; *see also* Section V.B.) Dr. Martine Rothblatt further confirmed in 2018 that payors covered PH-ILD patients' off-label use of Tyvaso, publicly stating to investors, in relevant part, that:

*[A]s you would expect, [Tyvaso is] not an inexpensive therapy, and payers don't just, like, blindly push the pay button on Tyvaso. Every patient is*

*carefully assessed by payers in ensuring that it's an appropriate patient that they're obligated to pay for and not an experimental patient.* Having said that, both through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the *kindness and generosity of certain payers around the country* who have gone ahead and upon the initiative of their physicians, *were able to enable some WHO Group III patients to benefit* [from Tyvaso and], there were unmistakable signals the some of the leading physicians in the field[,] I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, *"This drug works."*

(DTX0003, ("UTC 2018 Earnings Call") LIQ\_PH-ILD\_00000001 at LIQ\_PH-ILD\_00000010 (emphasis added).)

446. Mr. Dean Bunce, one of UTC's designated corporate witnesses, similarly testified that UTC's drug safety reports documented off-label prescription sales of Tyvaso to treat PH-ILD patients. (Bunce Depo. Tr. at 22:15-25; *id.* at 20:25-21:14.) From 2014 to 2018, UTC's drug safety reports describe at least four instances of Tyvaso being sold and used to treat PH-ILD patients. (DTX0175, FDA Adverse Event Reporting System (available at <https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis>) (LIQ\_PH-ILD\_00148745).) Mr. Bunce even admitted to having personal knowledge of doctors prescribing Tyvaso off-label to treat PH-ILD. (Bunce Depo. Tr. at 20:25-21:14.)

447. For these reasons, and based on the sale of Tyvaso, the subject matter of claims 1-11 and 15-19 was the subject of a commercial offer for sale, rendering these claims for invalid for prior sale.

448. UTC may argue that UTC did not sell Tyvaso to be used for the invention claimed in claims 1-11 and 15-19. This does not prevent application of the on-sale bar. This is because the on-sale bar is not limited to end-user transactions; it may be triggered by a commercial offer

or sale to intermediaries, including distributors, such as physicians prescribing and payors actually paying or the use of Tyvaso for the treatment of PH-ILD.

449. UTC may also argue that nobody at the time recognized that off-label sales of Tyvaso to treat PH-ILD patients embodied the claimed invention. This also does not prevent application of the on-sale bar. What matters is not whether physicians and payers fully understood at the time of the sale that the subject matter of claims 1-11 and 15-19 had been obtained, but whether the sale of Tyvaso relates to a product or method that embodies the claimed invention. As discussed herein, Tyvaso embodies the invention of claims 1-11 and 15-19.

**C. Claims 1-11 and 15-19 of the '327 Patent Are Anticipated by the Prior Art**

**1. Claims 1-4, 6, 8, 11, and 15-19 of the '327 Patent Are Anticipated by the February 2020 Press Release**

450. If the Court determines that the claims of the '327 patent are not entitled to the April 17, 2020 priority date of the '810 provisional, then UTC's February 24, 2020 press release titled "United Therapeutics Announces INCREASE Study of Tyvaso® Meets Primary and All Secondary Endpoints," reporting on the findings of the INCREASE trial, anticipate the claims of the '327 patent. (DTX0265, ("Feb. 2020 Press Release"), UTC\_LIQ00063612.)

451. The February 24, 2020 Press Release specifically discloses that the INCREASE trial exhibited "Tyvaso increas[ing] six-minute walk distance by 21 meters versus placebo (p=0.0043, Hodges-Lehmann estimate) after 16 weeks of treatment." (DTX0265, Feb. 2020 Press Release.) Dr. Smith confirmed that this statement denoted a "statistically significant difference between placebo and Tyvaso in six-minute walk distance." (Smith Depo. Tr. at 214:11-216:10.) The press release also reported that "[s]ignificant improvements were also observed in each of the study's secondary endpoints including reduction in the cardiac biomarker NT-proBNP, time to first clinical worsening event, change in peak 6MWD at Week 12, and change in trough 6MWD at

week 15.” (DTX0265, Feb. 2020 Press Release.) Dr. Smith confirmed that this statement reflects a statistically significant difference in these measured outcomes. (Smith Depo. Tr. at 215:21-216:10.) In the Press Release, Dr. Rothblatt announced that UTC achieved “highly statistically significant proof of efficacy” with the INCREASE Study. (DTX0265, Feb. 2020 Press Release.)

452. UTC’s February 24, 2020 Press Release also specifically discloses the following:

- “*INCREASE* was a phase III, multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study of Tyvaso in patients with pulmonary hypertension associated with interstitial lung disease. Enrollment into the study was completed in August 2019 with a total of 326 patients. Patients were randomized in a 1:1 Tyvaso (n=163) or placebo (n=163).”
- “Secondary objectives of the study included:
  - Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
  - Time to clinical worsening calculated as the time from randomization until one of the following criteria are met:
    - Hospitalization due to a cardiopulmonary indication
    - Decrease in 6MWD >15% from Baseline directly related to disease under study, at two consecutive visits, and at least 24 hours apart
    - Death (all causes)
    - Lung transplantation
  - Change in peak 6MWD from Baseline to Week 12
  - Change in trough 6MWD from Baseline to Week 15.”

453. The February 24, 2020 Press Release expressly directs its readers to the INCREASE trial because it reports on the INCREASE trial. (Anticipated Testimony of Dr. Channick.) A POSA would know the INCREASE study used Tyvaso®, the claimed dosing regimen and a pulsed inhalation device. (Anticipated Testimony of Dr. Channick.) This is because the Feb. 2020 Press Release specifically says INCREASE was a “clinical study of Tyvaso® (treprostinil) Inhalation Solution . . . .” (DTX0265, Feb. 2020 Press Release.) The Feb. 2020 Press Release also states that the results of INCREASE were “consistent with previous Tyvaso studies in PAH and known prostacyclin-related adverse events (see the discussion of adverse events below under ‘About Tyvaso’).” (DTX0265, Feb. 2020 Press Release.) Further, under “About Tyvaso” in the Feb. 2020 Press Release, it states “To learn more about Tyvaso, talk with your healthcare provider. Please see Full Prescribing Information, Patient Product Information, and the TD-100 and TD-300 TYVASO® Inhalation System Instructions for Use manuals at [www.tyvaso.com](http://www.tyvaso.com) or call 1-877-UNITHER (1-877-864-8437).” (DTX0265, Feb. 2020 Press Release.) Thus, the Press Release expressly directs POSAs to information about INCREASE and Tyvaso®, including dosing and the pulsed inhalation device. (Anticipated Testimony of Dr. Channick.)

454. Asserted Claim 1 is directed to a method of improving exercise capacity in patients with PH-ILD by administering at least 15 micrograms of inhaled treprostinil in a single administration event comprising at least 6 micrograms per breath. The Feb. 2020 Press Release, which reports on the INCREASE study, discloses the treatment of patients with PH-ILD using inhaled treprostinil (Tyvaso®) and discloses the use of “Tyvaso of up to 12 breaths per session, four times daily.” (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063612.) The dosing used in the INCREASE study was known by 2017. (DTX0008, 2017 INCREASE Study Description (LIQ\_PH-ILD\_00000185).) Further, the Feb. 2020 Press Release also directs readers to

instructions on the use of Tyvaso® by directing them to the “Full Prescribing Information, Patient Product Information” as well as other studies. (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063615.) The “Full Prescribing Information” for Tyvaso® discloses that it is intended to increase walk distance, is administered in an effective amount of at least 15 micrograms in a single administration event comprising at least 6 micrograms per breath which discloses those same limitations of claim 1 of the ’327 patent. (See DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010693, UTC\_PH-ILD\_010694.) The Feb. 2020 Press Release also discloses improvements in 6MWD, which as Dr. Peterson testified, a POSA would recognize as a proxy for improvements in exercise capacity. (Peterson Depo. Tr. at 145:9-12.) Thus, all the limitations of Asserted Claim 1 are anticipated by the Feb. 2020 Press Release. (Anticipated Testimony of Dr. Channick.)

455. Claims 2–3 are directed to improvements in 6MWD. Claim 2 requires a “statistically significant increase of a 6 minutes walk distance in a patient after 8 weeks, 12 weeks, or 16 weeks of administering.” (’327 patent at Claim 2.) The Feb. 2020 Press Release discloses an increase in 6MWD of 21 m with a p-value of 0.0043 at 16 weeks, which is statistically significant. (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063613.) It also discloses a “[c]hange in peak 6MWD from Baseline to Week 12” and “[c]hange in trough 6MWD from Baseline to Week 15.” A POSA would thus understand that the Feb. 2020 Press Release directly discloses the “statistically significant” increase in 6MWD required by claim 2 and directly discloses an increase in 6MWD by at least 10 m after 16 weeks required by claim 3. (Anticipated Testimony of Dr. Channick.)

456. Claim 4 is directed to a statistically significant reduction in plasma concentration of NT-proBNP in a patient after 8, 12, or 16 weeks of administering treprostinil. (’327 patent at Claim 4.) The Feb. 2020 Press Release reported “significant” improvements in NT-proBNP,



including a “[c]hange in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16,” which Dr. Smith confirmed refers to a statistically significant increase. (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063613; *see* Smith Depo. Tr. 215:21-216:10.) Because the Feb. 2020 Press Release discloses statistically significant improvements in the reduction of NT-proBNP it anticipates claim 4. (Anticipated Testimony of Dr. Channick.)

457. Claim 6 requires a “statistically significant reduction of at least one exacerbations of the interstitial lung disease.” The ’327 patent, Example 1 indicates that an exacerbation of ILD is a safety assessment. (’327 patent at 22:41-44.) The Feb. 2020 Press Release discloses that treatment with Tyvaso “in the INCREASE study was well tolerated and the safety profile was consistent with previous Tyvaso studies in PAH and known prostacyclin-related adverse events . . . .” (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063612–13.) The Feb. 2020 Press Release also quotes Dr. Rothblatt, who stated the INCREASE study provided a “statistically significant proof of efficacy while seemingly to avoid the safety issues that have plagued systemic therapeutics.” (*Id.* at UTC\_LIQ00063612.) Additionally, the Feb. 2020 Press Release discloses a statistically significant increase in 6-minute walk distance as discussed for claims 2-3 above, which correlates to a reduction in exacerbations of interstitial lung disease. Because the Feb. 2020 Press Release discloses that the INCREASE Study met all its primary and secondary endpoints, particularly the statistically significant improvement in 6MWD, it anticipates claim 6 of the ’327 patent. (Anticipated Testimony of Dr. Channick.)

458. Claims 7–8 are directed to the reduction of clinical worsening events. Claim 7 requires a “statistically significant reduction” while claim 8 specifies that the clinical worsening event comprises “at least one hospitalization for cardio-pulmonary indication and a decrease in a

6-minute walk distance by more than 15% compared to a baseline 6-minute walk distance prior to administering.” The Feb. 2020 Press Release reported significant improvements in time to first clinical worsening event, and further disclosed that the time to clinical worsening was calculated as the time from randomization until there is a “[h]ospitalization due to a cardiopulmonary indication” or “[d]ecrease in 6MWD>15% from Baseline.” (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063612; Smith Depo. Tr. at 215:2-216:10.) Further, Dr. Rothblatt described the INCREASE study as achieving “highly statistically significant proof of efficacy.” (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063613.) Because the Feb. 2020 Press Release discloses that the INCREASE Study met its primary and all its secondary endpoints, and specifically discloses time to clinical worsening, including specific parameters, it anticipates claims 7 and 8 of the ’327 patent. (Anticipated Testimony of Dr. Channick.)

459. Claim 11 requires the use of a pulsed inhalation device. The Feb. 2020 Press Release discloses that the INCREASE Study used “Tyvaso® (treprostinil) Inhalation Solution” to treat patients with PH-ILD. Because the administration of Tyvaso® requires a pulsed inhalation device, the Feb. 2020 Press Release anticipates claim 11. (DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010694; DTX0360, 2021 Tyvaso® Label at UTC\_PH-ILD\_010745.)

460. Claim 15 requires the use of an “effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg.” Claim 16 requires that the single inhalation administration event of Claim 15 “does not exceed 15 breaths by the patient.” The Feb. 2020 Press Release discloses the use of Tyvaso®, an inhaled treprostinil, to treat patients with PH-ILD. As described above with respect to claim 1, the Feb. 2020 Press Release also discloses the use of “Tyvaso of up to 12 breaths per session, four times daily” (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063612)

and directs readers to instructions on the use of Tyvaso by directing them to the “Full Prescribing Information, Patient Product Information” as well as other studies. (*Id.* at UTC\_LIQ00063615; *see also* DTX0072, 2017 Tyvaso® Label (LIQ\_PH-ILD\_00044770).) The “Full Prescribing Information” for Tyvaso discloses that it is intended to increase walk distance, is administered in an effective amount of at least 15 micrograms in a single administration event comprising at least 6 micrograms per breath. (*See* DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010693; UTC\_PH-ILD\_010694.)

461. Furthermore, the Feb 2020 Press Release discloses patients were administered a maximum of 12 breaths per treatment session, which a POSA would understand to mean a single administration event. (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063612.) Because a maximum of 12 breaths in a single inhalation administration event does not exceed 15 breaths by the patient, the Feb. 2020 Press Release anticipates claim 16 of the ’327 patent. (Anticipated Testimony of Dr. Channick.)

462. Claims 17–18 require varying improvements in 6MWD by the patient. Claim 17 requires an increase by “at least 10 m after 8 weeks of administering” and claim 18 requires an increase by “at least 15 m after 12 weeks of administering.” (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063612.) The Feb. 2020 Press Release discloses an increase in 6MWD of 21 m after week 16. It also discloses a “[c]hange in peak 6MWD from Baseline to Week 12” and “[c]hange in trough 6MWD from Baseline to Week 15.” (*Id.* at UTC\_LIQ00063613.) Because the Feb. 2020 Press Release discloses a 6MWD change of 21 m *after* week 16, it discloses a change of at least 10 m after week 8 and at least 15 m *after* week 12. Accordingly, a POSA would understand that the disclosure of the Feb. 2020 Press Release anticipates claim 17–18 of the ’327 patent. (Anticipated Testimony of Dr. Channick.)

463. Claim 19 requires an increase by at least 15 m after 16 weeks of administering. The Feb. 2020 Press Release discloses an increase in 6MWD of 21 m after week 16, anticipating claim 19. (DTX0265, Feb. 2020 Press Release at UTC\_LIQ00063612.)

464. UTC has taken the position that the Feb. 24, 2020 Press Release does not anticipate claim 1 and its dependents because a POSA would not reference it when administering inhaled treprostinil given its lack of detail and peer-review. (Anticipated Testimony of Dr. Nathan) Anticipation does not require access by a POSA to be an invalidating prior art reference. However, the Feb. 24, 2020 Press Release is the type of information a POSA would have been aware of. (Anticipated Testimony of Dr. Channick.) The press release contains a significant amount of detail, including specific data. (DTX0265, Feb. 2020 Press Release.) There is also no requirement that a POSA must reference only what is peer-reviewed. Clinicians receive direct emails and other communications reporting on significant events like those disclosed in the press release. (Anticipated Testimony of Dr. Channick.)

465. Furthermore, this position is inconsistent with the position taken by Drs. Nathan and Wertheim. Dr. Nathan has argued that direct infringement would occur when doctors followed the YUTREPIA label. Dr. Nathan also argued that where the YUTREPIA label lacked the requisite detail and peer-review to satisfy the asserted claims, a POSA would review other publicly available publications, abstracts, posters, or presentations discussing the results of the INCREASE study to understand the study's results because the YUTREPIA label referenced and relied upon the INCREASE study. (Anticipated Testimony of Dr. Nathan.) Dr. Wertheim has argued that the '327 patent was entitled to claim priority to the '810 provisional because even though Example 1 of the '810 provisional does not expressly reference the INCREASE trial, a POSA would nevertheless refer to the INCREASE trial to fill in the details needed to support the '327 patent's

priority claim. (Anticipated Testimony of Dr. Wertheim.) While the YUTREPIA label and '810 provisional do not mention INCREASE, the February 2020 Press Release explicitly directs its readers to the INCREASE study because it reports on the results of the INCREASE trial.

466. According to Drs. Nathan and Thisted, the dependent claims of the '327 patent do not require any measurement or determination of any result achieved by administering the claimed composition. (Anticipated Testimony of Dr. Nathan; Anticipated Testimony of Dr. Thisted.) Therefore, to anticipate the dependent claims of the '327 patent, including claims 2-4, 6, 8, 11, and 15-19, the February 2020 Press Release need not disclose the measurement or determination of any result achieved. Moreover, the Asserted Claims do not include a requirement that treprostinil be proven to be the cause of the recited results through the conduct of a placebo-controlled clinical trial or otherwise.

**2. Claims 1-3, 6-8, 11, and 15–19 of the '327 Patent Are Anticipated by Faria-Urbina 2018**

467. As discussed in Section V.C.6, Faria-Urbina 2018 describes a retrospective study of PH-ILD patients who were treated with inhaled treprostinil. Faria-Urbina 2018's dosing regimen is substantially similar to that of the 2009 Tyvaso® Label, and PH-ILD patients experienced statistically significant improvements in 6MWD and WHO functional class. (See Section V.C.6.)

468. According to Drs. Nathan and Thisted, the dependent claims of the '327 patent do not require any measurement or determination of any result achieved by administering the claimed composition. (Anticipated Testimony of Dr. Nathan; Anticipated Testimony of Dr. Thisted.) Therefore, to anticipate the dependent claims of the '327 patent, including claims 2, 3, 6-8, 11, and 15-19, Faria-Urbina 2018 need not disclose the measurement or determination of any result achieved. Moreover, the Asserted Claims do not include a requirement that treprostinil be proven

to be the cause of the recited results through the conduct of a placebo-controlled clinical trial or otherwise.

**a. Claim 1 of the '327 Patent is Anticipated by Faria-Urbina 2018**

**(1) Claim 1[a]: “A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising”**

469. A POSA would have found Faria-Urbina 2018 to anticipate Asserted Claim limitation 1[a]. (Anticipated testimony of Dr. Channick.) As discussed in Section V.C.6, Faria-Urbina 2018 retrospectively studied Group 3 PH patients who were administered inhaled treprostinil. Faria-Urbina 2018 reported statistically significant improvements in 6MWD and WHO functional class. (*See* Section V.C.6.)

**(2) Claims 1[b]-[d]**

470. As discussed in Section V.C.6, the dosing regimen described in Faria-Urbina 2018 is substantially similar to that of the 2009 Tyvaso® Label. Specifically, a POSA would interpret “three breaths (18µg) four times daily (72 µg/day)” (as described in Faria-Urbina 2018) as administering 6µg treprostinil per breath, which is exactly what claims 1[b]-[d] require (“comprises at least 6 micrograms per breath”). (Anticipated testimony of Dr. Channick.) Drs. Faria-Urbina and Waxman confirmed that patients received 6µg per breath, which is the standard Tyvaso dosing. (Faria-Urbina Depo. Tr. at 118:4-119:8; *see also* Waxman Depo. Tr. at 166:8-21.) Because patients initially received (18µg) per dosing session, this also meets the “an effective amount of at least 15µg” in a single administration event.

471. A POSA would also understand Faria-Urbina 2018’s description of “increas[ing] as tolerated . . . to achieve a dose of at least 9-12 breaths or more (~54µg) four times daily (~216µg/day)” to describe the range provided in claim limitations [b]- [d] “at least 15 micrograms up to a maximum tolerated dose” in a single administration event. (Anticipated testimony of Dr.

Channick.) As confirmed by Dr. Faria-Urbina, 9 breaths at 6µg per breath amounts to 54µg per single administration event. (Faria-Urbina Depo. Tr. at 119:23-120:4; *see also* Waxman Depo. Tr. at 98:22-99:15.) Dr. Faria-Urbina confirmed that patients who took 9 breaths received 54µg per treatment session and those who were able to tolerate 12 breaths received a maximum tolerated dose of 72µg per treatment session. (Faria-Urbina Depo. Tr. at 118:19-24; DTX0140, 2017 Waxman Tr. at 9:16-19.)

472. Based on the dosing information described in Faria-Urbina 2018, a POSA would find Asserted Claim limitations 1[b]-[d] anticipated. (Anticipated testimony of Dr. Channick.)

**b. Dependent Claims 2, 3, 6, and 15–19 Are Anticipated by Faria-Urbina 2018**

**(1) Claim 2**

473. Based on the statistical significance reported in Faria-Urbina 2018, a POSA would find claim 2 anticipated. (Anticipated testimony of Dr. Channick.)

474. As discussed in Section V.C.6, Faria-Urbina 2018 reported that WHO Group 3 patients experienced a statistically significant improvement in 6MWD. (*See also* Faria-Urbina Depo. Tr. at 130:18-21; DTX0140, 2017 Waxman Tr. at 14:14-15.) Specifically, CPFE patients experienced a statistically significant improvement in 6MWD, from 238±9 meters at baseline to 293±22 meters at follow-up, with a p-value of 0.018. (*See* DTX0505, Faria-Urbina 2018 Supplement at UTC\_PH-ILD\_219378; *see also* Section V.C.6.)

475. As discussed in Section V.C.7, Dr. Waxman's 2017 presentation further shows that Faria-Urbina 2018 studied 22 WHO Group 3 patients having PH-ILD (DTX077, 2018 Waxman Presentation at LIQ\_PH-ILD\_00101312); this presentation showed statistically significant improvements in 6-minute walk distance. (*Id.* at LIQ\_PH-ILD\_00101314; Waxman Depo. Tr. at 109:4-13.)

476. Because the results of Faria-Urbina 2018 disclose the same statistical significance within the same time frame described in claim 2, a POSA would find that the Faria-Urbina publication anticipated claim 2. (Anticipated testimony of Dr. Channick.)

**(2) Claim 3**

477. As discussed in Section V.C.7, Faria-Urbina 2018 discloses that the patients had an average increase of 65m in their 6MWD at follow up, which occurred at least 3 months after initiation of treatment. (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009940 (Table 2); Faria-Urbina Depo. Tr. at 132:6-9; Waxman Depo. Tr. at 109:4-16; DTX077, 2018 Waxman Presentation at LIQ\_PH-ILD\_00101314; DTX0140, 2017 Waxman Tr. at 13:20-21.) Based on this disclosure, a POSA would determine that Faria-Urbina 2018 meets the “at least 10 m improvement after 8 weeks, 12 weeks, or 16 weeks after administration” limitation in claim 3. (Anticipated testimony of Dr. Channick.)

**(3) Claim 6**

478. Based on the WHO functional class improvements and the 6MWD data reported in Faria-Urbina 2018, a POSA would find claim 6 anticipated. (Anticipated testimony of Dr. Channick.)

479. The '327 patent defines an exacerbation of the interstitial lung disease as “an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality.” ('327 patent at 22:12-15.) Dr. Waxman further testified that exacerbations would comprise worsening oxygenation and worsening shortness of breath, both of which demonstrate respiratory deterioration. (Waxman Depo. Tr. at 115:21-116:2.)

480. As discussed in Section V.C.7, Faria-Urbina 2018 reported that Group 3 PH patients demonstrated statistically significant improvements in 6MWD and WHO functional class. If a patient demonstrates a statistically significant improvement in functional class, a POSA would



conclude that a statistically significant reduction in exacerbations would have also occurred, thereby anticipating claim 6. (Anticipated testimony of Dr. Channick; Waxman Depo. Tr. at 115:15-116:18.)

481. Further, because Faria-Urbina 2018 also disclosed a statistically significant improvement in the 6MWD test, this improvement would reflect a statistically significant reduction in the exacerbation of the interstitial lung disease, i.e., a reduction respiratory deterioration, thereby also anticipating claim 6. (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009936.)

482. Faria-Urbina 2018 also described a decrease in dyspnea (i.e., shortness of breath) in patients treated with inhaled treprostinil. (*Id.* at UTC\_PH-ILD\_009940 (Table 2).) Given that worsening oxygenation and shortness of breath are signs of significant respiratory deterioration, and Faria-Urbina 2018 demonstrates a decrease in shortness of breath, Faria-Urbina 2018 anticipates claim 6. (Anticipated testimony of Dr. Channick.)

#### **(4) Claim 7**

483. The '327 patent states that “clinical worsening event(s) may include one or more of hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death or a lung transplantation.” ('327 patent at 19:57-60.)

484. As discussed in Section V.C.7, Faria-Urbina 2018 reported Group 3 PH patients experienced statistically significant improvements in 6MWD. Given the '327 patent's definition of “clinical worsening,” a POSA would find that Faria-Urbina 2018 anticipates claim 7. (Anticipated testimony of Dr. Channick.) Under the '327 patent's definition of “clinical worsening,” a POSA would view a statistically significant increase in 6MWD as demonstrating a statistically significant reduction of a clinical worsening event involving 6MWD. (Anticipated testimony of Dr. Channick.) That is, because patients' 6MWD increased over the study period by

a statistically significant amount, there was no “reduction” of 6MWD by more than 15% from a baseline value. (Anticipated testimony of Dr. Channick.)

**(5) Claim 8**

485. Claim 8 further defines the “clinical worsening” claimed in claim 7 as “one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.” (’327 patent at Claim 8.) For the same reasons discussed above for claim 7, as they pertain to the statistically significant increase in the 6MWD test, a POSA would find that Faria-Urbina 2018 anticipates claim 8. (Anticipated testimony of Dr. Channick.)

**(6) Claim 11**

486. Because Faria-Urbina 2018 used inhaled treprostinil (Tyvaso®), administered by a pulsed nebulizer, a POSA would find claim 11 anticipated. (Anticipated testimony of Dr. Channick.)

**(7) Claim 15**

487. As discussed in Section V.C.7, Faria-Urbina 2018 describes administration of inhaled treprostinil in terms of dosing. Because Faria-Urbina 2018 describes “a single inhalation administration event” ranging from 18µg to 72 µg, a POSA would understand that this range falls within “15 µg to 100 µg” and, thus, anticipates claim 15. (Anticipated testimony of Dr. Channick.)

**(8) Claim 16**

488. As discussed in Section V.C.7, Faria-Urbina 2018 describes the dosing regimen administered to Group 3 PH patients. Because patients in Faria-Urbina 2018 received approximately 12 breaths per single administration event, a POSA would find that Faria-Urbina 2018 anticipates claim 16. (Anticipated testimony of Dr. Channick.)

**(9) Claim 17**

489. As discussed in Section V.C.7, Faria-Urbina 2018 describes the 6MWD results Group 3 PH patients experienced after receiving inhaled treprostinil. Because patients in Faria-Urbina 2018 experienced an increase in 6MWD of 65 m at follow-up (which was no less than 3 months post-initial administration), Because this is greater than the 10m increase after 8 weeks of the administration, a POSA would find that Faria-Urbina 2018 anticipates claim 17. (Anticipated testimony of Dr. Channick.)

**(10) Claim 18**

490. As discussed in Section V.C.7, Faria-Urbina 2018 describes the 6MWD results Group 3 PH patients experienced after receiving inhaled treprostinil. Because patients in Faria-Urbina 2018 experienced an increase in 6MWD of 65 m at follow-up (which was no less than 3 months post-initial administration), Because this is greater than the 15m increase after 12 weeks of the administration, a POSA would find that Faria-Urbina 2018 anticipates claim 18. (Anticipated testimony of Dr. Channick.)

**(11) Claim 19**

491. As discussed in Section V.C.7, Faria-Urbina 2018 describes the 6MWD results Group 3 PH patients experienced after receiving inhaled treprostinil. Because patients in Faria-Urbina 2018 experienced an increase in 6MWD of 65 m at follow-up (which was no less than 3 months post-initial administration), Because this is greater than the 15m increase after 16 weeks of the administration, a POSA would find that Faria-Urbina 2018 anticipates claim 19. (Anticipated testimony of Dr. Channick.)

**D. Claims 1-11 and 14-19 of the '327 Patent Are Inherently Anticipated by the Prior Art**

**1. Faria-Urbina 2018 Inherently (and Literally) Anticipates Claims 1-3, 6-8, 11, and 15-19**

492. As discussed above in Section VIII.C.2, Faria-Urbina 2018 literally anticipates claims 1-3, 6-8, 11, and 15–19. A POSA would also find these claims inherently anticipated by Faria-Urbina 2018. (Anticipated testimony of Dr. Channick.)

493. Dr. Waxman testified that the inhaled treprostinil dosing in INCREASE was the same as Faria-Urbina 2018. (Waxman Depo. Tr. at 166:8-15, 166:19-21; *see also id.* at 167:20-169:11; *see also* DTX0349, May 5, 2020 RIN-PH-201 Clinical Study Report Inhaled Treprostinil (UTC\_PH-ILD\_010356) (“INCREASE Final Study Report”) at UTC\_PH-ILD\_010382.) Dr. Waxman also testified that the patient population in the INCREASE study was the same as Faria-Urbina 2018. (Waxman Depo. Tr. at 224:16-25; *see also id.* at 225:1-23.) Dr. Waxman further testified that the dosing in INCREASE (which is the same as Faria-Urbina 2018) led to the results obtained in INCREASE. (*Id.* at 211:15-20, 211:22-24.) And finally, Dr. Waxman testified that the results of the INCREASE Study proved that, based on his work reported in Faria-Urbina 2018, he was “right,” that inhaled treprostinil will be effective to treat PH-ILD patients. (*Id.* at 229:23-231:6.)

494. The “Treatment Regimen and Follow-Up” section of Faria-Urbina 2018 indicates that PH-ILD patients received an initial dose of “three breaths (18 µg) four times daily (72 µg/day).” (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937.) After that, Faria-Urbina 2018 describes increasing the dose of inhaled treprostinil “as tolerated by three additional breaths (18 µg) per dosing session every 3-7 days to achieve a dose of at least 9-12 breaths or more (≥54 µg) four times daily (≥216 µg/day)[.]” (*Id.*) Inhaled treprostinil was the only drug evaluated because Faria-Urbina 2018 discloses, and Dr. Waxman confirmed, that patients were excluded if

“another PH-specific drug [was] added in a period <3 months from iTRE initiation.” (*Id.*; Waxman Depo. Tr. at 96:16-97:4, 97:6.)

495. With this dosing, Faria-Urbina 2018 reports that “out of 22 [PH-ILD] patients . . . 21 improved (or maintained) functional class from baseline to follow-up, after treatment with iTRE. Of these 21 patients: 19 improved SpO<sub>2</sub>; 10 had follow-up with 6MWT—all of them showing improvement in the distance walked.” (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009939.)

496. The INCREASE study administered inhaled treprostinil in the following manner: “Treprostinil for inhalation solution (0.6 mg/mL) was delivered via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath . . . The subject could then gradually increase their dose to reach a minimum of 3 breaths and titrate to a target dose of 9 breaths and a maximum dose of 12 breaths QID during waking hours, as clinically tolerated.” (DTX0349, INCREASE Final Study Report at UTC\_PH-ILD\_010381-83.)

497. Based on this dosing—and as confirmed by Dr. Waxman (Waxman Depo. Tr. at 211:15-20, 211:22-24)—the INCREASE study demonstrated improving the exercise capacity of a PH-ILD patient (DTX0363, NEJM Publication at UTC\_PH-ILD\_010793 (“Mixed-model repeated-measures analysis showed that the least squares mean difference between the treprostinil group and the placebo group in the change from baseline in peak 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001) (Table 2 and Fig. S1)”), as well as obtaining a statistically significant increase in the 6MWD test of a PH-ILD patient (*id.*), a statistically significant reduction in an exacerbation of interstitial lung disease (*id.* at UTC\_PH-ILD\_010796 (“Significantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (43 [26.4%] vs. 63 [38.7%]; P = 0.02 by Fisher’s exact test)”), and a statistically significant reduction in clinical worsening events due to interstitial lung

disease. (*Id.* (“Fewer patients in the treprostinil group than in the placebo group had a first occurrence of clinical worsening that involved hospitalization for a cardiopulmonary indication (18 [11.0%] vs. 24 [14.7%];  $P = 0.41$ ).”).)

498. Because Faria-Urbina 2018 and the INCREASE study evaluated administered inhaled treprostinil by the same route of administration, to the same patient population, and with the same dosing regimen, the same results disclosed in the INCREASE study will necessarily and inevitably occur when a POSA follows the same dosing and same patient population disclosed in Faria-Urbina 2018. (Anticipated testimony of Dr. Channick; *see also* DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937.)

499. This is especially so because claim 1 and its dependents do not require that every PH-ILD patient experience an improvement in exercise capacity. (Anticipated testimony of Dr. Channick.) Claim 1 and its dependents, instead, require improving exercise capacity in “a patient.” (’327 patent at Claim 1.) The Court construed “a” to mean “one *or* more,” and further stated that “each individual administration and increase, reduction, or improvement involves a single patient.” (D.I. 149 (Court’s Claim Construction Opinion) at 6 (emphasis added).) UTC also agreed to this construction. (*See* D.I. 139 (UTC Oct. 10, 2024 Letter to the Honorable Richard G. Andrews) at 1.)

500. No method of treatment results in *every* patient experiencing the desired clinical outcome. (Anticipated testimony of Dr. Channick.) This is borne out by the ’327 patent, which does not describe every patient as experiencing an improvement in exercise capacity. (Anticipated testimony of Dr. Channick.) Example 3 of the ’327 patent, for instance, provides the data from the INCREASE study and demonstrates that not every patient’s 6MWD increased; it, instead, reports the statistically significant difference in 6MWD between the treatment versus placebo

groups. (*See* '327 patent at Table 5.) The '327 patent also discloses statistically significant results for NT-proBNP (*see id.* at 5:36-39), statistically significant results for a reduction in exacerbations of interstitial lung disease (*see id.* at 22:45-49), a statistically significant reduction in clinical worsening (*see id.* at 26:65-27:1), statistically significant improvement in percent predicted FVC (*see id.* at Table 1), and that some patients experienced increases in meters walked (*see id.* at Table 5). Further, the '327 patent says that "21% of the patients discontinued the trial prematurely (before week 16)." (*See id.* at 36:34-36.) Thus, based on the results of Faria-Urbina 2018, obtained using the same dosing as in INCREASE, Faria-Urbina 2018 necessarily and inevitably anticipates claims 1-3, 6-8, 11, and 15-19.

501. According to Drs. Nathan and Thisted, the dependent claims of the '327 patent do not require any measurement or determination of any result achieved by administering the claimed composition. (Anticipated Testimony of Dr. Nathan; Anticipated Testimony of Dr. Thisted.) Therefore, to inherently anticipate the dependent claims of the '327 patent, including claims 2, 3, 6-8, 11, and 15-19, Faria-Urbina 2018 need not disclose the measurement or determination of any result achieved. Moreover, the Asserted Claims do not include a requirement that treprostinil be proven to be the cause of the recited results through the conduct of a placebo-controlled clinical trial or otherwise.

**2. Claims 4, 5, 9, and 10 of the '327 Patent Are Inherently Anticipated by Faria-Urbina 2018**

502. As demonstrated by the INCREASE study, following the dosing disclosed in Faria-Urbina 2018 necessarily and inevitably leads to various clinical outcomes. (Anticipated testimony of Dr. Channick.) Certain dependent claims of the '327 patent describe these clinical outcomes and are inherently anticipated by Faria-Urbina 2018. (Anticipated testimony of Dr. Channick.) For the same reasons discussed above for claims 1-3, 6-8, 11, and 15-19, because Faria-Urbina

2018 administered inhaled treprostinil to PH-ILD patients in the same manner, and in the same amounts as the later conducted INCREASE study, Faria-Urbina 2018 also inherently anticipates claims 4, 5, 9, and 10. (Anticipated testimony of Dr. Channick.)

503. According to Drs. Nathan and Thisted, the dependent claims of the '327 patent do not require any measurement or determination of any result achieved by administering the claimed composition. (Anticipated Testimony of Dr. Nathan; Anticipated Testimony of Dr. Thisted.) Therefore, to inherently anticipate the dependent claims of the '327 patent, including claims 4, 5, 9, and 10, Faria-Urbina 2018 need not disclose the measurement or determination of any result achieved. Moreover, the Asserted Claims do not include a requirement that treprostinil be proven to be the cause of the recited results through the conduct of a placebo-controlled clinical trial or otherwise.

**a. Claim 4: “The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.”**

504. Following the same dosing schedule described in Faria-Urbina 2018, patients with PH-ILD showed statistically significant reductions in NT-proBNP levels, as reported by the INCREASE study report and the NEJM Publication, which disclosed the results of the INCREASE study. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010817; DTX0349, RINPH- 201 Clinical 14 Study Report, Inhaled Treprostinil (UTC\_PH-ILD\_010356).) Faria-Urbina 2018 inherently anticipates claim 4 because the reduction in NT-proBNP necessarily and inevitably occurred by dosing Tyvaso® (inhaled treprostinil) in the same manner in both Faria-Urbina 2018 and the INCREASE study because inhaled treprostinil is the only study drug evaluated in both. (Anticipated testimony of Dr. Channick.)



- b. Claim 5: “The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.”**

505. The INCREASE study resulted in a mean reduction of NT-proBNP by  $-396.35 \pm 1904.90$  pg/mL in treated patients from baseline to week 16. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010797 (Table 2).) Based on this result, and for the same reasons as discussed above for claim 4, Faria-Urbina 2018 inherently anticipates claim 5. (Anticipated testimony of Dr. Channick.)

- c. Claim 9: “The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.”**

506. Using the same dosing as Faria-Urbina 2018 in PH-ILD patients, a post-hoc analysis of the INCREASE study published in the Lancet reported PH-ILD patients experiencing improvements in FVC, including statistically significant improvements in % predicted FVC in the Intent-to-Treat population. (See DTX0009, S. Nathan, et al., *Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study*, The Lancet Respir. Med, (2021), published online June 29, 2021 [https://doi.org/10.1016/S2213-2600\(21\)00165-X](https://doi.org/10.1016/S2213-2600(21)00165-X) ((LIQ\_PH-ILD\_00000216) (“Lancet 2021”) at LIQ\_PH-ILD\_00000217; *see also id.* at LIQ\_PH-ILD\_00000218; *see also id.* at LIQ\_PH-ILD\_00000220 (Fig. 1); *see also* DTX0363, NEJM Publication at UTC\_PH-ILD\_010825.) Based on this result, and for the same reasons described for claim 4, Faria-Urbina 2018 inherently anticipates claim 9. (Anticipated testimony of Dr. Channick.)

- d. Claim 10: “The method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.”**

507. Using the same dosing as Faria-Urbina 2018 in PH-ILD patients, the INCREASE study resulted in an improvement in FVC from 0mL (baseline) to 28.5mL (week 8) to 44.4mL (week 16), which was at least a 20 ml improvement in FVC by at least weeks 8, 12 or 16 after administering inhaled treprostinil. (See DTX0349, INCREASE Final Study Report at UTC\_PH-ILD\_010434.) For the same reasons as discussed above for claim 9, Faria- Urbina inherently anticipates claim 10. (Anticipated testimony of Dr. Channick.)

**3. Claims 1-11 and 14-19 of the '327 Patent Are Inherently Anticipated by the 2009 Tyvaso Label, the 2017 INCREASE Study Description, and Agarwal 2015**

508. As discussed above, the 2009 Tyvaso® Label (see Section V.A.2), the 2017 INCREASE Study Description (see Section V.D.7), and Agarwal 2015 (see Section V.C.3) all disclose administration of the same drug, by the same route of administration, using the same dosing regimen, to the same patient population, as the INCREASE study. All the clinical outcomes observed in the INCREASE study, and subsequently claimed in the '327 patent, will necessarily and inevitably occur when following the dosing regimen and teachings of any of the earlier 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015. (Anticipated testimony of Dr. Channick.)

509. According to Drs. Nathan and Thisted, the dependent claims of the '327 patent do not require any measurement or determination of any result achieved by administering the claimed composition. (Anticipated Testimony of Dr. Nathan; Anticipated Testimony of Dr. Thisted.) Therefore, to inherently anticipate the dependent claims of the '327 patent, including claims 2-11 and 14-19, the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015,

need not disclose the measurement or determination of any result achieved. Moreover, the Asserted Claims do not include a requirement that treprostinil be proven to be the cause of the recited results through the conduct of a placebo-controlled clinical trial or otherwise.

**a. Claim 1**

510. The 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 inherently anticipate claim 1's requirement of "a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising." (Anticipated testimony of Dr. Channick.) The results of the INCREASE study demonstrate that the dosing schedule described in the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 leads to statistically significant improvements in PH-ILD patients' 6MWD test, which equates to an improvement in exercise capacity. (Anticipated testimony of Dr. Channick.) Because the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 administered the same drug, by the same route of administration, with the same dosing regimen as the INCREASE study, to the same patient population<sup>6</sup>, the clinical outcomes observed will necessarily and inevitably lead to the claimed limitation. (Anticipated testimony of Dr. Channick.)

511. Additionally, the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 literally describe claim 1's requirement of "administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a

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<sup>6</sup> The 2009 Tyvaso® Label was indicated for PAH, not PH-ILD, patients. (See DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010692).

pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.” (Anticipated testimony of Dr. Channick.)

512. The 2009 Tyvaso® Label discloses the following dosing:

- DOSAGE AND ADMINISTRATION**-----
- Use only with the Tyvaso Inhalation System. (2.1)
  - Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. (2.1)
  - Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours. (2.1)
  - Initial dosage: 3 breaths [18 mcg] per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. (2.1)
  - Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated. (2.1)
  - Titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated. (2.1)

(DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010693.)

513. Based on the above-captioned 2009 Tyvaso® Label, a POSA would understand that “3 breaths [18 mcg] per treatment session” involves administering, by inhalation, 6 micrograms of treprostinil per breath (18 micrograms divided by 3 breaths). (Anticipated testimony of Dr. Channick.) To be sure, the 2009 Tyvaso® Label states “[a] single breath of Tyvaso delivers approximately 6 mcg of treprostinil.”<sup>323</sup> Thus, a POSA would find this portion of the 2009 Tyvaso® Label to expressly disclose claim 1’s requirement of “a single administration event that comprises at least 6 micrograms per breath.” (DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010693.)

514. Additionally, because “[18 mcg] per treatment session” in the 2009 Tyvaso® Label satisfies claim 1’s requirement of administering “an effective amount of at least 15 micrograms . . . in a single administration event,” a POSA would also find this portion of claim 1 expressly taught. (Anticipated testimony of Dr. Channick.) Moreover, because the 2009 Tyvaso® Label teaches that dosing can be increased to 9 breaths per treatment session, which is 54 mcg per “treatment

session” (DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010694), a POSA would find that this also meets the “an effective amount of at least 15 micrograms . . . in a single administration event” requirement. (Anticipated testimony of Dr. Channick.)

515. The 2017 INCREASE Study Description also describes the dosing of claim 1. (Anticipated testimony of Dr. Channick.) The 2017 INCREASE Study Description instructed administering “approximately 6 mcg per breath” of inhaled treprostinil to PH-ILD patients, which anticipates the “at least 6 micrograms per breath” limitation. (DTX0008, 2017 INCREASE Study Description at LIQ\_PH-ILD\_00000194.)

516. The 2017 INCREASE Study Description also instructs administering inhaled treprostinil at “a maximum of 12 breaths four times daily” (*id.*), which satisfies the “at least 15 micrograms” limitation of claim 1. (Anticipated testimony of Dr. Channick.)

517. Agarwal 2015 also discloses the limitations of claim 1. Because Tyvaso® was the only inhaled treprostinil available at this time, a POSA would have understood (based on the 2009 Tyvaso® Label) that 3 breaths four times daily equates to 3 breaths X 6 µg per session, or 18 µg in a single administration event. (Anticipated testimony of Dr. Channick; DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508 (Methods).) And, because only one patient reached 15 breaths per single administration event six months after initiating treatment (the other patients only reached 9 and 12 breaths), a POSA would have found the “at least 15 micrograms” limitation of claim 1 inherently anticipated by Agarwal 2015. (Anticipated testimony of Dr. Channick.)

**b. Claim 2**

518. The INCREASE study demonstrated that, following its dosing regimen, PH-ILD patients experience a statistically significant increase in 6MWD. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010793.) Following the same dosing described by the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 will inherently anticipate claim 2 because

(as shown by the INCREASE study) PH-ILD patients will necessarily and inevitably experience a statistically significant increase in 6MWD. (Anticipated testimony of Dr. Channick; DTX0363, NEJM Publication at UTC\_PH-ILD\_010790.)

**c. Claim 3**

519. For the same reasons discussed for claim 2, a POSA would find that the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 inherently anticipate claim 3. (Anticipated testimony of Dr. Channick.)

**d. Claim 4**

520. The INCREASE study demonstrated that, following its dosing regimen, PH-ILD patients experience a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of administering. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010793-94.) Following the same dosing schedule described in the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 will inherently anticipate claim 4 because (as shown by the INCREASE study) PH-ILD patients will necessarily and inevitably experience statistically significant reductions in NT-proBNP levels in the same time intervals as reported by the NEJM paper. (Anticipated testimony of Dr. Channick; DTX0363, NEJM Publication at UTC\_PH-ILD\_010817.)

**e. Claim 5**

521. For the same reasons as discussed above for claim 4, a POSA would find that the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 inherently anticipate claim 5. (Anticipated testimony of Dr. Channick.)

**f. Claim 6**

522. The INCREASE study demonstrated that, following its dosing regimen, PH-ILD patients experience a statistically significant reduction in at least one exacerbation of the interstitial

lung disease. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010796.) Following the same dosing described in the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 will inherently anticipate claim 6 because (as shown by the INCREASE study) PH-ILD patients will necessarily and inevitably experience statistically significant reductions of exacerbations of the disease. (Anticipated testimony of Dr. Channick; DTX0363, NEJM Publication at UTC\_PH-ILD\_010796.)

**g. Claim 7**

523. The INCREASE study demonstrated that, following its dosing regimen, PH-ILD patients experience a statistically significant reduction of clinical worsening events due to the interstitial lung disease. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010797 (Table 2).) Following the same dosing schedule described in the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 will inherently anticipate claim 7 because (as shown by the INCREASE study) PH-ILD patients will necessarily and inevitably experience statistically significant reductions in clinical worsening. (Anticipated testimony of Dr. Channick; DTX0363, NEJM Publication at UTC\_PH-ILD\_010817 (Figure S5); *see also id.* at UTC\_PH-ILD\_010794.)

**h. Claim 8**

524. For the same reasons discussed above for claim 7, the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 inherently anticipate claim 8. (Anticipated testimony of Dr. Channick; DTX0363, NEJM Publication at UTC\_PH-ILD\_010792.)

**i. Claim 9**

525. The INCREASE study demonstrated that, following its dosing regimen, PH-ILD patients experience a statistically significant improvement in FVC after 8 weeks, 12 weeks or 16 weeks of administration. (DTX0363, NEJM Publication at UTC\_PH-ILD\_010825 (Table S6); *see also* DTX0009, Lancet 2021 at LIQ\_PH-ILD\_00000216, -217.) Following the same dosing

described in the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015, and based on the INCREASE study, will inherently anticipate claim 9 because (as shown by the INCREASE study) PH-ILD patients will necessarily and inevitably experience statistically significant improvements in FVC. (Anticipated testimony of Dr. Channick; DTX0009, Lancet 2021 at LIQ\_PH-ILD\_00000216, -217; *see also id.* at LIQ\_PH-ILD\_00000218.)

**j. Claim 10**

526. For the same reasons as discussed above for claim 9, the 2009 Tyvaso® Label, the 2017 INCREASE Study Description, and Agarwal 2015 inherently anticipate claim 10. (Anticipated testimony of Dr. Channick.)

**k. Claim 11**

527. Because Section 2.1 of the 2009 Tyvaso® Label states “Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of the Optineb-ir Model ON-100/7 (an ultrasonic, *pulsed-delivery* device) and its accessories,” the 2009 Tyvaso® Label anticipates, literally and inherently, claim 11. (Anticipated testimony of Dr. Channick; DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_010694 (§ 2.1.) (emphasis added).)

528. A POSA would understand Agarwal 2015 and the 2017 INCREASE Study Description to disclose the use of Tyvaso® because it was the only form of inhaled treprostinil available in 2015 and 2017. (Anticipated testimony of Dr. Channick.) As discussed above, the 2009 Tyvaso® Label makes clear that Tyvaso® is administered via a pulsed inhalation device. (*See* Section V.A.2.) Thus Agarwal 2015 and the 2017 INCREASE Study Description, anticipate, literally and inherently, claim 11. (Anticipated testimony of Dr. Channick.)

**l. Claim 14**

529. Because a POSA would understand that inhaled treprostinil could be delivered via either a nebulizer or dry powder inhaler, the 2009 Tyvaso® Label, Agarwal 2015, and the 2017



INCREASE Study Description inherently anticipate claim 14. (Anticipated testimony of Dr. Channick.)

**m. Claim 15**

530. Because the 2009 Tyvaso® Label, 2017 INCREASE Study Description, and Agarwal 2015 disclose administration, in a single event, of 6 µg per breath at an initial dose of 3 breaths four times daily, with a target dose of 9 breaths four times daily, a POSA would have found these three references to inherently anticipate claim 15, which requires delivery of at least 18 µg of treprostinil in a single inhalation administration event to 54 µg of treprostinil in a single administration event. (Anticipated testimony of Dr. Channick.)

**n. Claim 16**

531. Because the 2009 Tyvaso® Label, 2017 INCREASE Study Description, and Agarwal 2015 disclose administration of 6 µg per breath at an initial dose of 3 breaths four times daily, with a target dose of 9 breaths four times daily, these references inherently anticipate claim 16, as 9 breaths “does not exceed 15 breaths.” (Anticipated testimony of Dr. Channick.)

**o. Claim 17**

532. For the same reasons discussed above for claim 2, the 2009 Tyvaso® Label, 2017 INCREASE Study Description, and Agarwal 2015 inherently anticipate claim 17. (Anticipated testimony of Dr. Channick.)

**p. Claim 18**

533. For the same reasons discussed above for claim 2, the 2009 Tyvaso® Label, 2017 INCREASE Study Description, and Agarwal 2015 inherently anticipate claim 18. (Anticipated testimony of Dr. Channick.)

**q. Claim 19**

534. For the same reasons discussed above for claim 2, the 2009 Tyvaso® Label, 2017 INCREASE Study Description, and Agarwal 2015 inherently anticipate claim 19. (Anticipated testimony of Dr. Channick.)

**IX. OBVIOUSNESS**

**A. Claims 9-10 and 14 of the '327 Patent Are Obvious Over the February 2020 Press Release in Combination with the '793 Patent and Saggar 2014**

535. If the Court determines that the claims of the '327 patent are not entitled to the April 17, 2020 priority date of the '810 provisional, then a POSA would have been motivated to combine the February 2020 Press Release with the '793 patent and Saggar 2014 since all three publications describe the use of treprostinil to treat PH, including PH-ILD. (Anticipated Testimony of Dr. Channick.) Moreover, a POSA would have had a reasonable expectation of success in achieving the limitations of claims 9, 10, and 14 of the '327 patent. (Anticipated Testimony of Dr. Channick.)

536. A discussion of the full disclosure of the February 2020 Press Release is provided in Section V.D.9.

537. A discussion of the full disclosure and teachings of the '793 patent is provided in Section V.C.8.

538. A discussion of the full disclosure and teachings of Saggar 2014 is provided in Section V.C.2.

**1. Claims 9-10 of the '327 Patent Are Obvious Over the February 2020 Press Release in Combination with the '793 Patent and Saggar 2014**

539. Claim 9 depends from claim 1 and additionally requires “a statistically significant improve[ment] of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks” of administering inhaled treprostinil. ('327 patent at Claim 9.) Claim 10 adds further

requirements, covering the “method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.” (*Id.* at Claim 10.)

540. Claims 9 and 10 of the ’327 patent are obvious over the February 2020 Press Release in combination with the ’793 patent and Saggar 2014 because a POSA would have been motivated to combine the February 2020 Press Release with the ’793 patent and Saggar 2014 as each of these publications describes the use of treprostinil to treat PH, including PH-ILD. (Anticipated Testimony of Dr. Channick.) Moreover, a POSA would have had a reasonable expectation of success in achieving the FVC limitations of claims 9 and 10 of the ’327 patent given the improvement reported in Saggar 2014. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000226; Rajeev Saggar Depo. Tr. at 134:5-16; Anticipated Testimony of Dr. Channick.)

541. A POSA would be motivated to replace the use of parenteral treprostinil in Saggar 2014 and the February 2020 Press Release with inhaled treprostinil because it is the same medication, the same molecule, would be more convenient to use, and a POSA in 2020 would understand that using inhaled treprostinil should decrease the V/Q mismatch safety concerns associated with systemic vasodilator administration. (Anticipated Testimony of Dr. Channick.) In fact, it was commonly understood that inhaled treprostinil may be a better alternative to other pulmonary hypertension treatments in PH-ILD patients because the treprostinil is delivered directly to well-ventilated perfused areas of the lung and should avoid some of the potential for V/Q mismatch with systemic delivery of treprostinil. (Anticipated Testimony of Dr. Channick.)

542. The dosage of treprostinil in Saggar 2014 and the February 2020 Press Release is different in part because the route of administration is different. (Anticipated Testimony of Dr. Channick.) A POSA would know that the dosage would need adjusted to a different dosing scheme

for the use of inhaled treprostinil. (Anticipated Testimony of Dr. Channick.) A POSA would look to the February 2020 Press Release which discloses that patients received “[t]reatment with Tyvaso of up to 12 breaths per session, four times daily” to determine the dose of inhaled treprostinil. (DTX0403, Feb. 2020 Press Release at UTC\_PH-ILD\_112152.) For POSAs unfamiliar with Tyvaso’s dosing scheme, the February 2020 Press Release includes a section titled “About Tyvaso® (treprostinil) Inhalation Solution” which directs readers to the full prescribing information and other sources containing information about Tyvaso:

The risk information provided here is not comprehensive. To learn more about Tyvaso, talk with your healthcare provider. Please see Full Prescribing Information, Patient Product Information, and the TD-100 and TD-300 TYVASO® Inhalation System Instructions for Use manuals at [www.tyvaso.com](http://www.tyvaso.com) or call 1-877-UNITHER (1-877-864-8437).

(DTX0403, Feb. 2020 Press Release at UTC\_PH-ILD\_112154-55.)

543. The difference in dosage and route of administration do not preclude a POSA from relying on Saggart 2014. (Anticipated Testimony of Dr. Channick.) Furthermore, the fact that Saggart 2014 treats a subset of PH-ILD patients does not discount its relevance to a POSA seeking to treat PH-ILD patients with inhaled treprostinil as a whole. (Anticipated Testimony of Dr. Channick.)

544. Dr. Nathan and UTC have taken the position that claims 9-10 are not obvious by the February 2020 Press Release in combination with Saggart 2014 because there was no motivation to combine those two references with a reasonable expectation of success in obtaining the results in claims 9-10. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan has argued that a POSA would not be motivated to combine Saggart 2014 with the February 2020 Press Release with a reasonable expectation of success because the dosage, route of administration, and disease are different and a POSA would not expect to observe the same effects between two studies after changing so many variables. (Anticipated Testimony of Dr. Nathan.) However, a POSA is

expected to apply common sense and knowledge to solve problems and given the knowledge of a POSA in 2020, the differences between Saggar 2014 and the February 2020 Press Release do not change the motivation or expectations of a POSA when seeking to treat PH-ILD patients with inhaled treprostinil and improve FVC in light of both references. (Anticipated Testimony of Dr. Channick.)

545. UTC and its experts maintain that the disease population of Saggar 2014 is different enough that a POSA would not be motivated to combine Saggar 2014 with the February 2020 Press Release with a reasonable expectation of success. (Anticipated Testimony of Drs. Nathan and Thisted.) To the extent there is any difference in the severity of PH in the PH-ILD patients disclosed in Saggar 2014 and the February 2020 Press Release, such differences would not dissuade a POSA from combining the references and have a reasonable expectation of success doing so. (Anticipated Testimony of Dr. Channick.)

546. Dr. Nathan has argued that a POSA would not expect the combination of the February 2020 Press Release and Saggar 2014 to succeed in part because he equates a “reasonable hypothesis to test” with “hope” and claims it is different from an expectation of success. (Anticipated Testimony of Dr. Nathan.) A reasonable expectation of success does not require the absolute predictability of success and both Drs. Deng’s and Waxman’s confirmation that there was a “reasonable assumption” to test and a need for inhaled treprostinil to be investigated suggests more than just an abstract possibility. (Deng Depo. Tr. at 23:15-24:5; Waxman Depo. Tr. at 50:6-51:10.) The combination of the February 2020 Press Release, Saggar 2014, and the ’793 patent is grounded in prior knowledge, data, and scientific reasoning, which implies some degree of anticipated success. (Anticipated Testimony of Dr. Channick.)

547. Dr. Nathan has argued that the 1% difference in % predicted FVC achieved in Saggar 2014 is negligible in the context of such a small patient population and without a placebo group for comparison. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan has further argued that because the 1% change in Saggar 2014 is not statistically significant, it discloses a lack of change in FVC. (Anticipated Testimony of Dr. Nathan.) However, Saggar 2014 does not need to disclose a statistically significant change in FVC to render the statistically significant change claimed in the '327 patent obvious. It is enough that a POSA would be motivated to achieve a statistically significant change in FVC with a reasonable expectation of success. A POSA would have a reasonable expectation of success of achieving at least the 1% change in FVC observed in Saggar 2014. (Anticipated Testimony of Dr. Channick.)

548. The 0.77% and 1.07% increases in FVC described in the '327 patent at Weeks 8 and 16, respectively, and reported in the supplemental materials for the NEJM article on the INCREASE trial, is entirely consistent with the 1% improvement in % predicted FVC reported in Saggar 2014. (Anticipated Testimony of Dr. Channick.) Statistical significance with respect to changes in FVC is only reported in the '327 patent for difference compared to placebo and not reported for improvement in FVC within the treprostinil treatment group. Thus, a POSA would understand that treating PH-ILD patients with treprostinil, whether parenteral or inhaled, should result in a similar improvement. (Anticipated Testimony of Dr. Channick.) This is the value achieved and disclosed in the '327 patent, making it obvious in light of the Saggar 2014 disclosure when combined with the successful use of inhaled treprostinil disclosed in the February 2020 Press Release. (Anticipated Testimony of Dr. Channick.)

549. Dr. Nathan has claimed that the combination of the February 2020 Press Release and Saggar 2014 do not teach every element of claims 9 and 10. (Anticipated Testimony of Dr.

Nathan.) However, a finding of obviousness does not require that the combination of the February 2020 Press Release and Saggar 2014 explicitly teach every element of claims 9 and 10. All that is required is that the prior art provides a POSA the motivation to practice the limitations described in a claim with a reasonable expectation of success. Thus, with respect to claims 9-10 of the '327 patent, and to the extent the Court finds that the '327 patent is not entitled to the April 17, 2020 filing date of the '810 provisional, a person of ordinary skill in the art would have been motivated to combine the Feb. 2020 Press Release with Saggar 2014 in view of their knowledge and background, and had a reasonable expectation of success in developing the claimed method of treating PH-ILD of claims 9-10 of the '327 patent based upon such information. (Anticipated Testimony of Dr. Channick.)

**2. Claim 14 of the '327 Patent is Obvious Over the February 2020 Press Release in Combination with the '793 Patent**

550. Claim 14 depends from claim 11 which is directed at “[t]he method of claim 1, wherein said administering is performed by a pulsed inhalation device.” ('327 patent at Claim 11.) Claim 14 additionally requires that “the pulsed inhalation device is a dry powder inhaler comprising treprostinil or a pharmaceutically acceptable salt thereof.” (*Id.* at Claim 14.)

551. Claim 14 of the '327 patent is obvious over the February 2020 Press Release in combination with the '793 patent and Saggar 2014. There is a motivation to combine, as each of these publications describes the use of treprostinil to treat PH, including PH-ILD. (Anticipated Testimony of Dr. Channick.) A POSA would also have a reasonable expectation of success when replacing the nebulizer used in the February 2020 Press Release with a dry powder inhaler and dry powder formulation of treprostinil as described in the '793 patent. (Anticipated Testimony of Dr. Channick.)

552. Dr. Nathan and UTC take the position that there is no motivation to combine the '793 patent with the February 2020 Press Release because they do not think that a POSA would believe a dry powder to be interchangeable with a nebulizer or that a dry powder in the context of the '793 patent would be expected to improve exercise capacity in a patient with PH-ILD as discussed in the February 2020 Press Release. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan's opinion is refuted by the '793 patent itself, which discloses only results using a nebulized formulation of treprostinil and specifically claims a dry powder formulation of treprostinil. ('793 patent, Examples 1 and 2 (8:63-18:20); '793 patent, cl. 4, 6, 7.) Claim 4 of the '793 patent claims a dry powder inhaler, while claim 6 of the '793 patent recites "wherein the formulation is a powder" and claim 7 discloses "wherein the powder comprises particles less than 5 micrometers in diameter." The specification describes that "[t]he inhalation device can be also a dry powder inhaler" and "[i]n such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter." ('793 patent, 7:22-26.)

553. Thus, the '793 patent demonstrates the interchangeability of a nebulized solution and a dry powder formulation. (Anticipated Testimony of Dr. Channick.)

554. Nonetheless, the dry powder inhaler does not need to be interchangeable with the nebulizer for a POSA to have the requisite motivation and reasonable expectation of success to use the dry powder inhaler. A POSA does not need to believe that a dry powder inhaler is "interchangeable with a nebulizer" but merely needs to have some motivation and reasonable expectation of success that a dry powder inhaler could be used. The '793 patent specifically provides this through its specification and claims. Furthermore, this Court already determined that the claimed method of treatment in the '793 patent was directed to all 5 Groups of PH use dry



powder formulations of treprostinil. (DTX0036, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755-RGA, D.I. 433 (D. Del. Aug. 31, 2022) (LIQ\_PH-ILD\_00001018) at 41 (“District Court Opinion”); *see United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 464 (D. Del. 2022), *aff’d*, 74 F.4th 1360 (Fed. Cir. 2023).)

555. It does not matter that the ’793 patent does not disclose a specific formulation of inhaled treprostinil for use with a dry powder inhaler or a model of dry powder inhaler. Claim 14 of the ’327 patent is not directed to a specific dry powder formulation. The ’793 patent describes both the treprostinil dosing information and the use of DPIs. (’793 patent at 7:22-26.) Since, this Court already found that a POSA with the ’793 patent would have been able to make and use the full scope of the claimed method of treatment in the ’793 patent using dry powder formulations of treprostinil and based on data obtained using a nebulized solution of treprostinil and a nebulized pulsed inhalation device, and the fact that the ’793 patent claims specifically claim a dry powder inhaler and formulation, a POSA would have a reasonable expectation of success when replacing the nebulizer used in the February 2020 Press Release with a dry powder inhaler and dry powder formulation of treprostinil, rendering claim 14 obvious. (*See United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 464 (D. Del. 2022), *aff’d*, 74 F.4th 1360 (Fed. Cir. 2023).)

**B. Claims 1-11 and 14-19 of the ’327 Patent Are Obvious Over Faria-Urbina 2018 in Combination with the ’793 Patent and Saggar 2014**

**1. A POSA Would Have Been Motivated to Combine Faria-Urbina 2018 with the ’793 Patent and Saggar 2014 with a Reasonable Expectation of Success**

556. A POSA as of April 2020 would have been motivated to combine and would have had a reasonable expectation of success in combining Faria-Urbina 2018 with the ’793 patent and Saggar 2014.

**a. A POSA Would be Motivated to Combine Faria-Urbina 2018 with the '793 Patent**

557. A discussion of the full disclosure of Faria-Urbina 2018 is provided in paragraphs 174-184.

558. Both the '793 patent and Faria-Urbina 2018 describe treating PH-ILD patients with inhaled treprostinil according to similar dosing schemes (i.e., between 15 and 90 µg in 3 breaths administered several times per day). (*See* DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937 (Treatment regimen and follow-up); *see* '793 patent at 18:21-31 (Claim 1).)

559. When deciding to treat pulmonary hypertension in PH-ILD patients with inhaled treprostinil, a POSA would look to Faria-Urbina 2018 and the '793 patent for motivation and for at least how to start prescribing the dose that should be used in PH-ILD patients. Physicians generally chose to follow the Tyvaso® dosing when treating patients with PH-ILD because the Tyvaso® dosing recommendation was what physicians were familiar with. (Waxman Depo. Tr. at 97:13-98:2; 98:18-21.) The same dosing scheme was used in the INCREASE study because the steering committee had experience with that approach in both PAH and PH-ILD patients. (Waxman Depo. Tr. at 97:13-98:2; 98:18-21.) Since the dosing disclosed in the '793 patent is the dosing in the 2009 Tyvaso® label that covers treating Group 1 PAH, a POSA would be motivated to combine the '793 patent which discloses a similar dosing scheme ((i.e., between 15 and 90 µg in 3 breaths administered several times per day) as Faria-Urbina 2018. (*See* DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937 (Treatment regimen and follow-up); *see* '793 patent at 18:21-31 (Claim 1).)

560. A full discussion of the disclosure of Saggar 2014 is provided in paragraphs 150-159.

561. Although Saggar 2014 administered treprostinil parenterally, and inhaled treprostinil was used in Faria-Urbina 2018 and the '793 patent, all these publications disclosed similar results with respect to hemodynamics and 6MWD. (*See* DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009936; *see also* DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000226; '793 patent at UTC\_PH-ILD\_009772.) This is not surprising because all three references used the same molecule, treprostinil, and whether administered systemically, like in Saggar 2014, or locally, like Faria-Urbina 2018 and the '793 patent, treprostinil still works as a vasodilator. Systemically administered treprostinil will vasodilate indiscriminately and inhaled treprostinil will vasodilate locally, in healthy portions of the lung. (Anticipated testimony of Dr. Channick; Waxman Depo. Tr. at 38:5-11.)

562. A POSA would be motivated to replace the parenteral administration of treprostinil in Saggar 2014 to the inhaled route of administration in Faria-Urbina 2018 and the '793 patent in order to minimize or avoid the issue of V/Q mismatch. Although Saggar 2014 did not observe V/Q mismatch issues, it was known that systemic delivery of a prostacyclin, like treprostinil, could result in V/Q mismatch. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000226; *see also id.* at LIQ\_PH-ILD\_00000228-229 (Safety/adverse events, Pulmonary function testing, 6MWD, and oxygen status), LIQ\_PH-ILD\_00000230-231 (Discussion).)

563. The '793 patent also discloses that the inhalation of a highly concentrated aerosol such as treprostinil can lead to “increased shunt flow or increase of low ventilation/perfusion (V/Q) areas.” ('793 patent at 11:38-40.) It notes that “[n]o significant increase in low V/Q areas or shunt fraction after inhalation of [soft mist inhaler treprostinil] was observed,” and states that this “proves an excellent intrapulmonary selectivity of [soft mist inhaler treprostinil.]” (*Id.* at 11:55-58.) A POSA would understand this to mean that the use of inhaled treprostinil likely does not

worsen V/Q mismatch and may be a better alternative for treating PH caused by interstitial lung disease compared to other pulmonary hypertension treatment alternatives because the treprostinil is delivered directly to well-ventilated and perfused areas of the lung. (Anticipated testimony of Dr. Channick.) Indeed, Drs. Saggar, Tapson, and Waxman confirmed that physicians believed inhaled treprostinil may be more successful in treating PH-ILD because the delivery method would not worsen V/Q mismatch. This, and the '793 patent's description of inhaled treprostinil as having "excellent tolerability at doses" and "well tolerated in concentrations up to 2000 mg/ml" and "in high doses (up to 90 µg)" would motivate a POSA to at least select inhaled treprostinil over other vasodilators and how to start prescribing the dose that should be used in PH-ILD patients. ('793 patent at 12:48-55.)

564. Dr. Waxman made several public presentations addressing V/Q mismatch and the benefits of inhaled treprostinil to avoid this issue. In the 2017 John Vane Presentation discussed in paragraphs 169-173 above, Dr. Waxman described that some studies have described systemic vasodilators as resulting in worsening V/Q mismatch, stating that they override the normal pathology in the lung and vasodilate everything. (DTX0140, 2017 Waxman Tr. at 8:9-19, 11:10-20; Waxman Depo. Tr. at 42:13-24.) He then pointed out that an optimal inhaled dose of treprostinil will target areas of the lung that have preserved V/Q. (DTX0140, 2017 Waxman Tr. at 11:10-20.) Dr. Waxman expanded on this during his deposition, explaining that a systemic vasodilator will deliver the drug to all areas of the lung because it goes wherever the blood flows and vasodilates areas of the lung indiscriminately. (See Waxman Depo. Tr. at 41:9-24.) However, an inhaled drug, and specifically inhaled treprostinil, will be delivered only to well-ventilated areas of the lung and will only vasodilate areas where the inhaled treprostinil is actually delivered. (See

*id.* at 41:25-42:6.) Dr. Waxman's 2017 presentation and testimony confirm that physicians believed inhaled treprostinil may be better than other prostacyclins before April 2020.

565. Accordingly, a POSA would be motivated by the positive results obtained in Saggar 2014, but employ the inhaled route of administration of Faria-Urbina 2018 and the '793 patent, and would do so with a reasonable expectation of success based on the comparable positive results observed in all these references in the same patient population.

**b. The State of the Art and the Knowledge of a POSA Before 2020 Also Motivates a POSA to Combine Faria-Urbina 2018 with the '793 Patent**

566. A POSA would have been motivated to combine Faria-Urbina 2018 with the '793 patent based on the state of the art prior to 2020, including at least U.S. Patent App Publication No. 2013/0096200 A1 ("Wade 200") and Parikh 2016, as well as the knowledge of a POSA at this time.

567. To the extent UTC contends that a POSA would not be motivated to use inhaled treprostinil to treat PH-ILD, their own Wade 200 published application from 2013, discussed in Section V.C above, proves otherwise. The disclosure of Wade 200 is provided in paragraphs 144-149. Moreover, UTC and its experts cannot state that a POSA would lack an expectation of success in treating PH-ILD with inhaled treprostinil. UTC filed a patent application in 2013 that expressly discloses the use of inhaled treprostinil to treat PH-ILD. (DTX0361, Wade 200 at Claims 1-2; [0012], [0020]; *see also* Wade Depo. Tr. at 32:14-33:17.) Thus, UTC's own patent application, Wade 200, also provides a POSA with a motivation and reasonable expectation of improving exercise capacity in patients with PH-ILD using inhaled treprostinil.

568. In addition to Wade 200, Parikh 2016 expressly discloses the use of inhaled treprostinil to treat PH-ILD patients as discussed in paragraphs 165-168. Parikh 2016 also reflected UTC's knowledge of off-label use of Tyvaso in PH-ILD patients. (Smith Depo. Tr. at

78:24-79:10. ) Thus, the successful results disclosed in Parikh 2016 provide a POSA with a reasonable expectation of successfully treating PH-ILD with inhaled treprostinil.

**c. The INCREASE Study and Statements from UTC Confirm that a POSA Would Have been Motivated to Combine Faria-Urbina 2018 with the '793 Patent**

569. The NEJM Publication cites to Faria-Urbina 2018 as motivation for conducting the study. (*See* DTX0363, NEJM Publication at UTC\_PH-ILD\_010791, -799.) It cites several other prior art references, including Agarwal 2015, stating:

Data from previously completed pilot studies suggest that inhaled treprostinil can improve hemodynamics and functional capacity in patients with group 3 pulmonary hypertension. Therefore, the objective of the INCREASE trial was to evaluate the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease.

(DTX0363, NEJM Publication at UTC\_PH-ILD\_010791.)

570. Even before the study was published, the INCREASE protocols and investigator brochure referenced Faria-Urbina 2018 as part of the rationale for further investigating the treatment of PH-ILD patients with inhaled treprostinil.

571. While not considered prior art, the INCREASE Study Protocol, discussed in paragraphs 223-231 above, confirms that UTC was motivated to treat PH-ILD with inhaled treprostinil to improve exercise capacity. In the protocol, UTC included a section titled “Rationale For Development of Study Drug in Disease/Condition” describing the rationale for treating patients with PH-ILD with inhaled treprostinil in order to improve exercise capacity. (*See* DTX0373, Original Protocol at UTC\_PH-ILD\_054899; DTX0401, Final Protocol at UTC\_PH-ILD-105100.) This section specifies that “[i]nhaled treprostinil is expected to directly target the more ventilated portion of the lungs in patients with WHO Group 3 PH minimizing the risk of ventilation perfusion mismatch and allowing for improvements in exercise capacity.” (*Id.*) It also lists Seeger 2013, Wang 2015, Bajwa 2016, and Agarwal 2015. (*See* DTX0373, Original Protocol

at UTC\_PH-ILD\_054899; DTX0401, Final Protocol at UTC\_PH-ILD-105100-01.) The data in Agarwal 2015 became part of Faria-Urbina 2018. (Waxman Depo. Tr.at 169:1-11.) Thus, based on prior art disclosures, UTC acknowledged not only a motivation to use inhaled treprostinil to treat PH-ILD, but a reasonable expectation that such administration will be successful.

572. The Investigator's Brochure for the INCREASE study, dated August 26, 2016, also disclosed the rationale for treating patients with PH-ILD with inhaled treprostinil. (DTX0387, Investigator Brochure UTC\_PH-ILD\_082805 at UTC\_PH-ILD\_082814.) The brochure is a guide to the clinical trial and is meant for the individual physicians that take part in the study. (Tapson Depo. Tr. at 80:1-9.) Investigator brochures provide motivation as to why a study is conducted, as well as what the expected outcome for the study is. (*Id.* at 80:12-19.) The rationale section provided investigators with the motivation behind the INCREASE study and set expectations for the study results. (*Id.* at 84:7-85:1.) The rationale section also disclosed Agarwal 2015 and Sagar 2014, among others, as references supporting the rationale for treating PH-ILD patients with inhaled treprostinil. (DTX0387, Investigator Brochure at UTC\_PH-ILD\_082813.) Again, based on prior art disclosures, UTC acknowledged not only a motivation to use inhaled treprostinil to treat PH-ILD, but a reasonable expectation that such administration will be successful.

573. Furthermore, UTC, including its CEO and other members of management, and the steering committee members did not doubt that the INCREASE Study would be successful. (*see also* Nathan Depo. Tr. at 41:12-23, 44:6-11, 159:14-160:25, 202:14-206:7, 222:25-224:5, 232:2-9; DTX0003, UTC 2018 Earnings Call at LIQ\_PH-ILD\_00000010.) Dr. Nathan did not recall his co-steering committee members or UTC ever expressing doubts that the INCREASE study would be successful, (Anticipated testimony of Dr. Nathan) and in fact, stated that, in 2019, he was "cautiously optimistic" that the INCREASE study would demonstrate positive results. (DTX0680,

S. Nathan, PH-ILD: past studies and future directions, presented at PFF Summit Nov. 9, 2019, <https://www.youtube.com/watch?v=ggHFReApqnk> (“PFF Summit 2019”) at 15:56.)

574. Dr. Nathan and his co-steering committee members for the INCREASE study, Drs. Waxman and Tapson, believed that Faria-Urbina 2018 and Agarwal 2015, amongst other studies disclosed in the NEJM Publication, served as justification for the INCREASE trial. (Anticipated testimony of Dr. Nathan.) The rationale in the protocol, which includes Agarwal 2015, provided the motivation and expectation as to what would happen in the clinical trial. (Tapson Depo. Tr. at 94:7-25.) In his 2017 presentation at the John Vane Symposium, Dr. Waxman confirmed that the data from Faria-Urbina 2018, which he presented, provided additional evidence for using Tyvaso® to treat PH-ILD patients. (Waxman Depo. Tr. at 93:9-14.) These statements made by the steering committee members confirm that a POSA would have been motivated to improve the exercise capacity of PH-ILD patients using inhaled treprostinil prior to April 2020.

575. Public statements made by UTC’s Chairman and CEO, Dr. Martine Rothblatt, specifically statements made during UTC’s earnings call for Q1 2018, which was held on May 2, 2018 also reflect the state of the prior art at the time. During the call, Dr. Rothblatt received a question regarding the rationale behind using Tyvaso in ILD. (DTX0003, UTC 2018 Earnings Call at LIQ\_PH-ILD\_00000009.) As part of her answer, Dr. Rothblatt responded:

[S]tarting with the COPD and ILD. Treprostinil, Tyvaso is not on label for patients with these indications. And as you would expect, it’s not an inexpensive therapy, and patients don’t just, like, blindly push the pay button on Tyvaso. Every patient is carefully assessed by payers in ensuring that it’s an appropriate patient that they’re obligated to pay for and not an experimental patient. Having said that, both through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit, there were unmistakable signals the some of the leading physicians in this field. ***I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, “This drug works.”*** In fact, they believe that this drug works even better in that



indication than in the Group I indication in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved *So with that kind of data, some of which has been presented in posters and maybe even publications -- I don't know, but I've definitely seen posters*, we went ahead and then had the statistics to power of the study for statistical significance, the one in the ILD population and the other in the COPD population, which are 2 distinct populations.

(*Id.* (emphasis added).)

Dr. Rothblatt's statement indicates that at least Dr. Waxman, among other physicians, used Tyvaso to treat PH-ILD patients prior to the May 2, 2018 date of the earnings call. Moreover, the fact that Dr. Rothblatt states she has seen "posters" and "papers" on this issue reflects acknowledgment of Faria-Urbina 2018 and Agarwal 2015 as they speak directly to the study of Tyvaso in PH-ILD patients. These statements provide motivation to combine.

576. Dr. Waxman's statements also confirm that a POSA would be motivated to combine the '793 patent, which discloses a method of treating Group 1 PAH patients with inhaled treprostinil, with Faria-Urbina 2018 in order to improve the exercise capacity of PH-ILD patients by treating them with inhaled treprostinil. Dr. Waxman also testified that there was "a lot of overlaps between the various groups when you look at the pathology there's overlap, when you look at the mediators that are circulating, there's overlap. When you look at the fundamental abnormalities of proliferation and abnormal cell death, there are overlaps, so it made sense again in my opinion, to study this drug [inhaled treprostinil] in other forms of pulmonary hypertension." (Waxman Depo. Tr. at 51:1-10.) Thus, a POSA would have been motivated to combine Faira-Urbina 2018 with the '793 patent and Saggar 2014 to improve the exercise capacity of PH-ILD patients using inhaled treprostinil.

**d. Non-Confidential Presentations Concerning Faria-Urbina 2018 as “Preliminary” and “Supportive Evidence” Confirm that a POSA Would Have Been Motivated to Combine Faria-Urbina 2018 and the ‘793 Patent with a Reasonable Expectation of Success**

577. The 2017 Recruitment Presentation, 2017 John Vane Presentation, and the 2018 Waxman Science Day Presentation, all discussed in Sections V.C.5, 7 and V.D.6 above, provide motivation to combine Faria-Urbina 2018 with the ‘793 patent and Saggar 2014 and further confirm that a POSA would have had a reasonable expectation of success, and that UTC did in fact have a reasonable expectation of success, that inhaled treprostinil could be used to improve exercise capacity in PH-ILD patients.

578. A discussion of the 2017 Recruitment Presentation is provided in paragraph 222.

579. The 2017 Recruitment Presentation was intended to be disclosed to clinicians. (DTX0384, 2017 Recruitment Presentation (UTC\_PH-ILD\_081749); Smith Depo. Tr. at 177:25-178:10.) The third slide of the presentation is titled “Supportive Evidence for Tyvaso in WHO Group 3 PH” referring to the data presented in Agarwal 2015. (DTX0384, 2017 Recruitment Presentation at UTC\_PH-ILD\_081752.) The following slides discuss Dr. Waxman’s data, and the “Discussion and Conclusion” slide contains the statement that “this study provides preliminary evidence supporting the safety and efficacy of inhaled treprostinil in the treatment of Group 3 PH with advanced lung disease complicated by pulmonary vascular remodeling.” (*Id.* at UTC\_PH-ILD\_081755.)

580. Thus, the 2017 Recruitment Presentation, relying on the same data contained in the Faria-Urbina 2018 publication, further confirms that a POSA would not only be motivated by Faria-Urbina 2018 to use inhaled treprostinil to treat PH-ILD and improve exercise capacity, but would do so with a reasonable expectation of success.

581. During his 2017 John Vane Presentation, discussed above in paragraphs 169-173, Dr. Waxman went through the data described above with respect to the Faria-Urbina 2018 paper. (Waxman Depo. Tr. at 68-93.) Dr. Waxman also discussed pulmonary vascular remodeling, which in his opinion, regardless of any other underlying disease, is where the pulmonary vascular disease lies. (DTX0140, 2017 Waxman Tr. at 3:18-4:10; Waxman Depo. Tr. at 71:25-72:9.) He further testified that in his opinion, “regardless of what associated diseases there are, if a patient develops pulmonary vascular disease and pulmonary hypertension, there’s overlap of the mechanism driving the disease and if we have a drug that works in one form, we should be able to re-purpose it to another.” (Waxman Depo. Tr. at 73:9-16.) Dr. Waxman concluded his talk stating:

And so to finish up, hopefully, you'll agree that at least these pilot findings do provide some support -- additional support that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered. And that these findings also provide additional evidence supporting more at – larger clinical trials in patients with this form of pulmonary vascular disease.

(Waxman Depo. Tr. at 91:7-13; DTX0140, 2017 Waxman Tr. at 17:8-16.)

582. Thus, the 2017 John Vane Presentation, relying on the same data contained in the Faria-Urbina 2018 publication, further confirms that a POSA would not only be motivated by Faria-Urbina 2018 to use inhaled treprostinil to treat PH-ILD and improve exercise capacity, but would do so with a reasonable expectation of success.

583. As described in paragraphs 185-186 above, Dr. Waxman also discussed the Faria-Urbina 2018 data at UTC’s Science Day in 2018. (Waxman Depo. Tr. 118:14-119:18.) The slide labeled LIQ\_PH\_ILD\_00101311 references the Faria-Urbina 2018 Study and the following slides describe the retroactive study, concluding that “[t]he findings of this pilot study provide preliminary evidence supporting the treatment of pre-capillary PH in patients with advanced lung disease.” (See DTX0077, 2018 Waxman Presentation at LIQ\_PH-ILD\_00101311–316.) Thus,

this 2018 presentation made on behalf of UTC, relying on the prior art Faria-Urbina 2018 publication, further confirms that a POSA would not only be motivated by Faria-Urbina 2018 to use inhaled treprostinil to treat PH-ILD and improve exercise capacity, but would do so with a reasonable expectation of success.

**e. A POSA Would Have a Reasonable Expectation of Successfully Combining Faria-Urbina 2018 with the '793 Patent to Improve the Exercise Capacity of Patients with PH-ILD**

584. Based on the disclosures of Faria-Urbina 2018, the '793 patent, the fact that physicians were already treating PH-ILD patients with inhaled treprostinil and seeing improvements in their exercise capacity, and that UTC believed treating PH-ILD patients with inhaled treprostinil would be successful, a POSA would have had a reasonable expectation of successfully improving the exercise capacity of PH-ILD patients by administering inhaled treprostinil.

585. The fact that Faria-Urbina 2018, actually treated PH-ILD patients with Tyvaso® and saw positive results in a number of parameters, including statistically significant results in the 6MWD test, would not only motivate a POSA to use Faria-Urbina 2018, but the actual positive results provide a POSA with a reasonable expectation of success. Indeed, the patients and data in Faria-Urbina provide “real world” experience of the use and success of inhaled treprostinil therapy in this patient population from at least 2009. (Waxman Depo. Tr. at 95:12-16.)

586. The '793 patent would also give a POSA a reasonable expectation of success. UTC told the FDA and the PTO that the '793 patent claims cover the FDA approved PH-ILD indication, which is directed to improving exercise capacity. Again, that acknowledgement by UTC not only demonstrates a reasonable expectation of success based on the '793 patent, but actual success, as physicians were regularly prescribing inhaled treprostinil to PH-ILD patients off-label prior to the

April 2020 filing date of the '327 patent, before the results of the INCREASE trial were published, and before Tyvaso® was approved for the treatment of PH-ILD.

**f. A POSA Would Have a Reasonable Expectation of Success of Combining Faria-Urbina 2018 with the '793 Patent Based on Doctor's Use of Tyvaso to treat PH-ILD Prior to 2020**

587. As discussed in paragraphs 107-141, POSAs were already administering PH-ILD patients with inhaled treprostinil long before April 2020. As evidenced by the positive studies discussed above, many physicians measured hemodynamics in these patients and also measured and saw significant improvements in exercise capacity. (Rajeev Saggar Depo. Tr. at 222:13-223:12; Rajan Saggar Sept. 17, 2024 Depo. Tr. at 20:17-21:18; Tapson Depo. Tr. at 40:5-21; Waxman Depo. Tr. at 204:24-205:5, DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508; DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009936.) The testimony of these clinicians from their real world practices again provide not only a reasonable expectation of success in using inhaled treprostinil to treat PH-ILD patients, but proof of actual success.

**g. UTC Cannot Dispute that A POSA Would Have a Reasonable Expectation of Successfully Improving Exercise Capacity in PH-ILD Patients**

588. To the extent UTC contends a POSA would not have a reasonable expectation of successfully treating a PH-ILD patient with inhaled treprostinil, its communications to the FDA and statements to the public prove otherwise.

589. For example, in his 2017 letter to the FDA submitted on behalf of UTC, Dr. Waxman represented that he had been “independently involved in the development of this research concept through work that is ongoing at The Center for Pulmonary Heart Disease at the Brigham and Women’s Hospital.” (Waxman Depo. Tr. at 186:6-10.) Dr. Waxman further represented to the FDA that “as we have seen in our preliminary studies, it is anticipated that patients with ILDPH may be more likely to benefit from prostacyclin therapy such as treprostinil.” (DTX0281, A.

Waxman's letter re Orphan Drug Designation to the FDA (November 15, 2017) (UTC\_LIQ00104555) at UTC\_LIQ00104556 (emphasis added).) The fact that Dr. Waxman "anticipated" PH-ILD patients will benefit represents more than a hope that inhaled treprostinil will be effective, it provides more than a reasonable expectation of success.

590. [REDACTED]

[REDACTED]

[REDACTED] (Smith Depo. Tr. at 194:3-23.) [REDACTED]

[REDACTED] (*Id.*)

Thus, UTC's 2017 statements to the FDA establish a POSA would not only have a motivation to use inhaled treprostinil as disclosed in Faria-Urbina 2018 and the '793 patent to treat PH-ILD, but that based on prior art disclosures, POSAs would also have a reasonable expectation of success.

591. Additional public statements from UTC confirm that a POSA would have a reasonable expectation of success in achieving the claims of the '327 patent long before April 2020. In 2018, when asked about the rationale for the INCREASE study, Dr. Martine Rothblatt, UTC's CEO, told investors that

both through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit [from Tyvaso and], there were unmistakable signals from some of the leading physicians in the field. I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, *'This drug works.'* ***In fact, they believe that this drug works even better in that indication than in the Group I indication, in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved.***

(DTX0003, UTC 2018 Earnings Call at LIQ\_PH-ILD\_00000010 (emphasis added).)

592. Her public statement that PH-ILD patients benefitted from inhaled treprostinil and that “This drug works” confirms that a POSA would have had a reasonable expectation of success prior to the April 2020 priority date of the ’327 patent.

593. [REDACTED]

594. These statements further confirm that a POSA would have a reasonable expectation of success in treating PH-ILD patients to improve exercise capacity using Tyvaso.

**2. Claim 1 of the ’327 Patent is Obvious Over Faria-Urbina 2018 in Combination with the ’793 Patent**

595. Each of the limitations of claim 1 are disclosed and rendered obvious by the combination of Faria-Urbina 2018 and the ’793 patent.

**a. Claim 1[a]: “A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising”**

596. As discussed in paragraphs 469-472 Faria-Urbina 2018 discloses claim element 1[a].

597. The ’793 also discloses claim 1[a] of the ’327 patent.

598. As discussed in paragraph 193 above, UTC admitted to the FDA that the ’793 patent claims cover the Tyvaso PH-ILD indication. (See DTX0028, Feb. 12, 2024, FDA Letter at

LIQ\_PH-ILD\_00000852.) Claim 1 of the '327 patent, according to the same letter UTC sent to the FDA, also covers claim 1 of the '327 patent. Additionally, a POSA would have known that hemodynamic improvements such as significant decreases in PVR and mPAP, as shown in Table 2 of the '793 patent, correlate with improvements in exercise capacity. (*See* paragraph 203 above.) Therefore, the '793 independently discloses a method of improving exercise capacity in patients with PH-ILD.

599. Although both Faria-Urbina 2018 and the '793 patent independently meet the limitation of claim 1[a], a POSA would have been motivated to combine Faria-Urbina 2018 with the '793 patent's method of treatment to arrive at claim 1 of the '327 patent. (Anticipated testimony of Dr. Channick.) Both Faria-Urbina 2018 and the '793 patent are directed to the use of inhaled treprostinil for the same disease, PH-ILD. Further, Faria-Urbina 2018 achieved improvements in exercise capacity in PH-ILD patients by treating them with inhaled treprostinil identical to the dosing scheme disclosed and claimed in the '793 patent (i.e., between 15 and 90  $\mu\text{g}$  in 3 breaths administered several times per day). (*Id.*; DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937 (Treatment regimen and follow-up); *see* '793 patent at 8:1-2.) Because the results in Faria-Urbina 2018 demonstrated improvements in exercise capacity, a POSA would have had a reasonable expectation of success when combining the '793 patent with Faria-Urbina 2018. (Anticipated testimony of Dr. Channick.) Since both references describe improvements in exercise by administering inhaled treprostinil to patients with PH-ILD, and because the combination discloses a method of improving the exercise capacity of a patient having PH-ILD, the combination renders claim 1 of the '327 patent obvious.



- b. Claim 1[b]-[d]: “administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.”**

600. Although both Faria-Urbina 2018 and the '793 patent independently meet claim limitations 1[b]-[d], a POSA would have been motivated to achieve the results disclosed in Faria-Urbina 2018 with the dosing scheme disclosed in the '793 patent and would have had a reasonable expectation of success in doing so. (Anticipated testimony of Dr. Channick.) The dosing scheme in Faria-Urbina 2018 and the dosing disclosed in claim 1 of the '793 patent are the same as the dosing required in claim 1 of the '327 patent. (*See* paragraphs 177-78, 195, 558-559.)

601. A POSA would understand Faria-Urbina 2018's description of “increas[ing] as tolerated . . . to achieve a dose of at least 9-12 breaths or more (~54µg) four times daily (~216µg/day)” to describe the range provided in claim limitations [b]-[d] “at least 15 micrograms up to a maximum tolerated dose” in a single administration event. (Anticipated testimony of Dr. Channick.) As confirmed by Dr. Faria-Urbina, 9 breaths at 6µg per breath amounts to 54µg per single administration event. (Faria-Urbina Depo. Tr. at 119:23-120:4; *see also* Waxman Depo. Tr. at 98:22-99:15.) Dr. Faria-Urbina confirmed that patients who took 9 breaths received 54µg per treatment session and those who were able to tolerate 12 breaths received a maximum tolerated dose of 72µg per treatment session. (Faria-Urbina Depo. Tr. at 118:19-24.) During his 2017 presentation at the John Vane Symposium, Dr. Waxman also confirmed that “[a]ll of the patients were started in the usual way, on inhaled treprostinil, with starting with three breaths four times daily and increased over time to an initial goal of 9 to 12.” (DTX0140, 2017 Waxman Tr. at 9:16-19.)

602. Thus, Faria-Urbina 2018 discloses claim limitations 1[b]-[d].

603. Claim 1 of the '793 patent covers a “method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension” an “effective single event dose comprise[d] from 15 micrograms to 90 micrograms of treprostinil” “delivering in 1 to 3 breaths.” ('793 patent at Claim 1.) Moreover, claim 1 of the '793 patent is directed to delivering 15 mcg of treprostinil in a single administration event. Delivering 15 mcg at 1 or 2 breaths, as claimed in '793 patent claim 1, meets the “at least 6 mcg per breath” limitation of claim 1 of the '327 patent. Thus, claim 1 of the '793 patent also meets the limitations of claims 1[b]-[d] of the '327 patent.

604. Additionally, the dosing for Tyvaso® is the same for both treatment of Group 1 PAH and Group 3 PH-ILD (both of which are described in the '793 patent). (DTX0360, 2021 Tyvaso® Label (UTC\_PH-ILD\_010744) at UTC\_PH-ILD\_010744.) And the dosing of Tyvaso® in the 2021 Label is the same as that provided in the 2009 Label. (DTX0357, 2009 Tyvaso® Label (UTC\_PH-ILD\_010692) at UTC\_PH-ILD\_010693.) Thus, Faria-Urbina 2018 combined with the '793 patent renders claim 1 obvious.

605. UTC may contend that the “therapeutically effective single dose” in claim 1 of the '793 patent refers only to a dose required to have a hemodynamic impact, which UTC maintains would be different from the amount needed to improve exercise capacity in a PH-ILD patient because the amount would vary with the patient and severity of the disease. But the teachings of the '793 patent are not confined to its claims. Nor does the '793 patent limit the treatment of a PH patient to a single dose. Indeed, the '793 patent describes dosing between 15-90 ug in 1-3 breaths, which a POSA would know requires titration. (See '793 patent at Claim 1.)

**3. Dependent Claims 2-11 and 14-19 of the '327 Patent Are Obvious Over Faria-Urbina 2018 in Combination with the '793 Patent and Saggar 2014**

**a. Dependent Claims 2-3**

606. Dependent claim 2 requires a “statistically significant increase of a 6 minutes walk distance in a patient after 8 weeks, 12 weeks, or 16 weeks” and claim 3 requires an increase in 6MWD “by at least 10 m after 8 weeks, 12 weeks, or 16 weeks” of administering inhaled treprostinil. ('327 patent at Claims 2–3.) Faria-Urbina 2018 in combination with the '793 patent discloses dependent claims 2-3 of the '327 patent.

607. Table S4 of the Faria-Urbina 2018 Supplementary Materials describes a statistically significant increase in 6MWD, from  $238 \pm 9$  meters at baseline to  $293 \pm 22$  meters at follow-up, in PH-CPFE, which is PH-ILD (p-value of 0.018). (DTX0505, Faria-Urbina 2018 Supplement (UTC\_PH-ILD\_219375) at UTC\_PH-ILD\_219378.) By demonstrating a statistically significant increase in 6MWD, this data from the Faria-Urbina 2018 Supplement makes obvious claims 2 and 3.

608. Faria-Urbina 2018 also reported in Table 2 that eleven patients who had a follow-up with the six-minute walk test after three months of treatment showed a statistically significant improvement in their six-minute walk distances. (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009940 (Table 2).) Table 2 shows that the average increase in 6MWD was 65 meters and reported a p value of 0.022, which is statistically significant. (*Id.*) Faria-Urbina 2018 also notes that all patients were followed “for at least 3 months” which anticipates the “after 8 weeks, 12 weeks, or 16 weeks” portion of claims 2 and 3. (DTX0348, Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at UTC\_PH-ILD\_009937.) Because the 6MWD p-value was 0.022, this provided a statistically significant improvement in the patient’s 6MWD after 8 weeks, 12, weeks or 16 weeks as required by claim 2. Additionally, because Faria-Urbina 2018 discloses that the patients had an

average increase of 65m in their 6MWD at follow up it meets the “at least 10 m improvement” limitation of claim 3.

609. UTC may contend that Faria-Urbina 2018 does not meet the limitations of claims 2-3 because it includes a non-homogenous population of Group 3 PH patients. However, the 6MWD results of PH-ILD patients within the Faria-Urbina 2018 patient population also meet the limitations of claims 2 and 3. Claim 1 only states that the patient population includes “a patient having pulmonary hypertension associated with interstitial lung disease,” *i.e.*, PH-ILD patients. (’327 patent at Claim 1.) Table 4 of the ’327 patent is titled “Characteristics of the Patients at Baseline” and it provides a breakdown of the cause of lung disease in the patients. (*Id.* at Table 4.) Among the listed causes is combined pulmonary fibrosis and emphysema (which is often abbreviated in medical literature as “CPFE”). (*Id.*) CPFE is a subset of PH-ILD. (Anticipated testimony of Dr. Channick.) To be sure, the original and final INCREASE protocols list the indication as “Pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE).” (DTX0373, 2015 INCREASE protocol (UTC\_PH-ILD\_054882) at UTC\_PH-ILD\_054885; DTX401, 2017 INCREASE Protocol (UTC\_PH-ILD\_105083) at UTC\_PH-ILD\_105086.) Thus, the statistically significant result obtained in CPFE patients disclosed in Faria-Urbina 2018 render claims 2 and 3 obvious.

610. Because the ’793 patent discloses the same drug, administered by the same route of administration, using the same dosing scheme to Faria-Urbina 2018, and in a PH-ILD population, a POSA would have been motivated to combine Faria-Urbina 2018 with the ’793 patent to further evaluate inhaled treprostinil’s impact on 6MWD in PH-ILD patients. (Anticipated testimony of Dr. Channick.) Specifically, Table 3 of the ’793 patent discloses that 15 pulmonary fibrosis

patients (i.e. PH-ILD patients) were part of the study. ('793 patent at Table 3 (Etiology of pulmonary hypertension where pulmonary fibrosis is category (f)).) The '793 patent also discloses positive hemodynamic results (treprostinil inhalation led to “maximal decreases of PVR to  $76.5 \pm 4.7\%$  (30  $\mu\text{g}$ ),  $73.7 \pm 5.8\%$  (60  $\mu\text{g}$ ),  $73.3 \pm 4.3\%$  (90  $\mu\text{g}$ ) and  $65.4 \pm 4.1\%$  (120  $\mu\text{g}$ ) of baseline values” and “[c]ardiac output was increased to a maximum of  $106.8 \pm 3.2\%$  (30  $\mu\text{g}$ ),  $122.9 \pm 4.3\%$  (60  $\mu\text{g}$ ),  $114.3 \pm 4.8\%$  (90  $\mu\text{g}$ ) and  $111.3 \pm 3.9\%$  (120  $\mu\text{g}$  TRE).”) which correlate to an improvement in exercise capacity. (*Id.* at 15:48-60, Figs. 8, 9; anticipated testimony of Dr. Channick.) Therefore, a POSA reading the '793 patent would have a reasonable expectation of success in combining Faria-Urbina 2018 with the '793 patent and treating PH-ILD patients with inhaled treprostinil in order to achieve the 6MWD results required by claims 2 and 3.

**b. Dependent Claims 4-5**

611. Claims 4 and 5 disclose “[t]he method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering[.]” and “[t]he method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering[.]” respectively. ('327 patent at Claims 4-5.) A POSA would have been motivated to combine the teachings of Faria-Urbina 2018 and the '793 patent with Saggar 2014 to arrive at the limitations in claims 4 and 5 and would have had a reasonable expectation of success in doing so.

612. In Saggar 2014, patients treated with parenteral treprostinil saw their BNP (brain natriuretic peptide) levels fall from 558 pg/ml to 228 pg/ml, a difference of 330 pg/ml, after 12 weeks and a p-value of 0.004. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000230 (Table 4).) Because BNP and NT-proBNP are indicators of disease severity in PH, there is a positive correlation between the two biomarkers. (Anticipated testimony of Dr. Channick.) There is no

clear advantage in using one biomarker over the other and a POSA would have understood that Sagggar 2014's statistically significant reduction of BNP levels is equivalent to a statistically significant reduction in NT-proBNP levels. (See DTX0086, Robert P. Frantz et al, *Baseline NT-proBNP correlates with change in 6-minute walk distance in patients with pulmonary arterial hypertension in the pivotal inhaled treprostinil study TRIUMPH-I*, 31 J. Heart & Lung Transplantation 811, 812 (2012) (available at [https://www.jhltonline.org/article/S1053-2498\(12\)01076-5/fulltext](https://www.jhltonline.org/article/S1053-2498(12)01076-5/fulltext)) (LIQ\_PH-ILD\_00101518).) Indeed, Dr. Rajan Sagggar testified that BNP and NT-proBNP can be viewed as congruent. (Rajan Sagggar Sept. 17, 2024 Depo. Tr. at 65:23-25.) Further, because positive results in 6MWD and hemodynamics were observed in PH-ILD patients in both parenteral and inhaled routes of treprostinil administration, a POSA would reasonably expect to achieve a statistically significant reduction in NT-proBNP as well as a reduction of at least 200 pg/ml after 8, 12 or 16 week of the administration as observed in Sagggar 2014, when administering treprostinil via inhalation as in Faria-Urbina 2018 and the '793 patent. (Anticipated testimony of Dr. Channick.)

613. Furthermore, Wade 200 correlates parenteral treprostinil with inhaled treprostinil. Wade 200 discloses both parenteral treprostinil and inhaled treprostinil in the context of treating PH-ILD and that an effective dose would be between 5-500 mcg "inhaled treprostinil per day." (DTX0361, Wade 200 at [0013].) Wade 200 also measure BNP and it expressly discloses that "[s]ubjects receiving Treprostinil **will show improvements** in the studied criteria . . . ." (DTX0361, Wade 200 at [0082]-[0087] (emphasis added).) UTC, via Wade 200, is stating that all of these measured endpoints will improve using treprostinil. Wade 200 thus motivates one to combine Faria-Urbina 2018, with the '793 patent and Sagggar 2014 with an expectation of success.

614. Additionally, a statistically significant improvement would have been obvious given the state of the art. Statistical significance is merely a matter of adequately powering a study with a sufficient number of patients, reflecting study design and sample size. The '327 patent did not identify a novel therapeutic effect but merely replicated what was already known in Faria-Urbina 2018 by evaluating the same drug, administered by the same route of administration, using the same dosing, in the same PH-ILD population. (Anticipated testimony of Dr. Channick.) The '327 patent simply studied more PH-ILD patients than Faria-Urbina 2018. Given that statistical significance is a matter of mathematical power, and physicians were seeing benefits in treating PH-ILD patients with inhaled treprostinil, a statistically significant change in any metric is obvious in light of the prior art.

615. Thus, the combination of Faria-Urbina 2018, the '793 patent and Saggar 2014 renders claims 4 and 5 obvious.

616. UTC may contend that a POSA would not be able to predict how changing both the dosage and administration route for treprostinil would affect the results described in Saggar 2014 and in view of Saggar 2014's small sample size and lack of control arm. However, the sample size is not disqualifying as prior art and a POSA would not simply disregard relevant clinical reports due to sample size. In fact, patient case studies and retrospective reviews are common and important sources of information and evidence in clinical practice. The clinical results seen in Saggar 2014 are actual results and therefore a POSA would consider them relevant to treating PH-ILD patients with inhaled treprostinil. The combination of Faria-Urbina 2018, the '793 patent, and Saggar 2014 and thus, claims 4-5 are still rendered obvious.

**c. Dependent Claim 6**

617. Claim 6 is directed to a “method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.” (’327 patent at Claim 6.)

618. The ’327 patent defines an exacerbation of the interstitial lung disease as “an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality.” (*Id.* at 22:12-15.) Exacerbations can include worsening oxygenation and worsening shortness of breath, both of which demonstrate respiratory deterioration. (Anticipated testimony of Dr. Channick; Waxman Depo. Tr. at 115:21-116:2.)

619. Functional class refers to the World Health Organization (WHO) functional class system, which measures the patient’s ability to perform physical activities and is directly tied to the severity of PH symptoms. (Anticipated testimony of Dr. Channick.) WHO FC I represents a “normal” person without any functional issues, whereas WHO FC IV represents someone with severely impaired function. (*Id.*; Waxman Depo. Tr. at 52:8-16.) In PH-ILD patients, PH and ILD are interdependent: worsening ILD (including exacerbations) can drive worsening PH and a decline in functional class, while improvement in PH (as reflected in functional class) can reduce exacerbations. (Anticipated testimony of Dr. Channick.) If a treatment like inhaled treprostinil improves functional class, it mitigates the cardiopulmonary strain that contributed to exacerbations and reduced 6MWD, thereby reducing the risk of an exacerbation.

620. As explained above in paragraphs 478-482, Faria-Urbina 2018 discloses the “wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease” limitation. To the extent UTC argues Faria-Urbina 2018 does not anticipate claim 6, it renders claim 6 obvious in combination with the ’793 patent and Saggar 2014.



621. Faria-Urbina 2018 reported that Group 3 PH patients demonstrated “significant improvement in functional class ( $n = 22$ , functional class III-IV 82 vs. 59%,  $p = 0.041$ ).” (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009936.) Table 2 of Faria-Urbina provides the results of the WHO FC assessment and confirms the changes were statistically significant. (*See id.* at UTC\_PH-ILD\_009940.) Metrics such as WHO-FC and 6MWD reflect clinical exacerbations include worsening oxygenation and worsening shortness of breath. (Anticipated testimony of Dr. Channick; Waxman Depo. Tr. at 115:15-116:18.) Accordingly, if a patient demonstrates a statistically significant improvement in functional class, a POSA would conclude that a statistically significant reduction in exacerbations to also occur.

622. Faria-Urbina 2018 also disclosed a statistically significant improvement in the 6MWD test. (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009936.) This improvement would reflect a statistically significant reduction in the exacerbation of interstitial lung disease, i.e., a reduction respiratory deterioration.

623. Faria-Urbina 2018 further described a decrease in dyspnea (i.e., shortness of breath) in patients treated with inhaled treprostinil. (*Id.* at UTC\_PH-ILD\_009940 (Table 2).) Given that worsening oxygenation and shortness of breath are signs of significant respiratory deterioration, and that Faria-Urbina 2018 demonstrates a decrease in shortness of breath, Faria-Urbina 2018 discloses the limitations of claim 6. (Anticipated testimony of Dr. Channick.)

624. Saggar 2014 also disclosed statistically significant improvements in 6MWD (mean 59 m;  $p < 0.001$ ), along with improvements in dyspnea, also known as shortness of breath, which were measured using the University of California San Diego Shortness of Breath (UCSD SOB) questionnaire and Short Form Health Survey (SF-36), respectively. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000228-229.) The patients’ USCD SOB scores changed from 87 to 73.1 with a

p value of 0.002, patients' SF-36 MCS scores increased from 38 to 33.2 with a p-value of 0.005 indicating improvements in shortness of breath. (*Id.*)

625. An improvement in shortness of breath as well as an improvement in 6MWD, demonstrates that there is a reduction in respiratory deterioration due to alveolar abnormalities. (*See Waxman Depo. Tr. at 116:3-18.*) Thus, it would have been obvious to a POSA that administration of treprostinil would result in a statistically significant reduction in at least one exacerbation of ILD.

626. While Saggar 2014 uses parenteral treprostinil, for the reasons discussed in paragraph 613, a POSA would have been motivated to combine its teachings with those of Faria-Urbina 2018 and the '793 patent since all three publications describe the use of treprostinil to treat PH, including PH-ILD. A POSA would have a reasonable expectation of success because Faria-Urbina 2018 and Saggar 2014 to reach a method resulting in a statistically significant reduction in exacerbations because both references report improvements in 6MWD, a proxy for respiratory function and clinical status which suggests reductions in respiratory deterioration. (Anticipated testimony of Dr. Channick.) Additionally, Saggar 2014 shows a statistically significant improvement in shortness of breath, which demonstrates a reduction in respiratory deterioration.

627. Because improvements in shortness of breath and improvements in 6MWD were observed with the use of parenteral treprostinil, a POSA would be motivated to monitor exacerbations when treating a patient with PH-ILD with inhaled treprostinil to determine if a similar effect occurred. The similarities in patient population, drug, and observed clinical benefits would lead a POSA to expect that the inhaled formulation could achieve comparable outcomes. By combining the disclosures of these three references, a POSA would have had a reasonable expectation of success in achieving the limitation of Asserted Claim 6 of the '327 patent.

628. A statistically significant reduction in exacerbations would also have been obvious given the state of the art. Statistical significance is merely a matter of adequately powering a study with a sufficient number of patients, reflecting study design and sample size. The '327 patent did not identify a novel therapeutic effect but merely replicated what was already known in Faria-Urbina 2018 by evaluating the same drug, administered by the same route of administration, using the same dosing, in the same PH-ILD population. (Anticipated testimony of Dr. Channick.) The '327 patent simply studied more PH-ILD patients than Faria-Urbina 2018.

**d. Dependent Claims 7-8**

629. Claim 7 is directed to “[t]he method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease[]” and claim 8 is directed to “[t]he method of claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.” ('327 patent at Claims 7-8.)

630. Paragraphs 483-484 above discuss how Faria-Urbina 2018 anticipates claims 7-8. To the extent UTC argues Faria-Urbina 2018 does not anticipate claims 7-8, it renders claim 7-8 obvious in combination with the '793 patent and Saggar 2014.

631. The '327 patent specification defines “clinical worsening” as including “one or more of hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death or a lung transplantation.” ('327 patent at 19:57-60, 30:52-60.)

632. Faria-Urbina 2018 reported that, at baseline, patients demonstrated a 6MWD of  $243 \pm 106$  meters; at follow-up, these patients showed a 6MWD of  $308 \pm 109$  ( $p = 0.022$ ). (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009940 (Table 2).)

633. Table S4 from the Faria-Urbina 2018 Supplement also demonstrates that the CPFE patients, a subset of PH-ILD patients, experienced a statistically significant increase in 6MWD (p-value of 0.018):  $238 \pm 9$  meters at baseline and  $293 \pm 22$  meters at the three-month follow-up. (DTX0505, Faria-Urbina 2018 Supplement (UTC\_PH-ILD\_219375) at UTC\_PH-ILD\_219378 (CPFE patients).)

634. Based on the '327 patent's definition of "clinical worsening," a POSA would understand that a statistically significant *increase* in 6MWD indicates a statistically significant reduction of a clinical worsening event involving 6MWD as required by claims 7 and 8. That is, because patients' 6MWD increased over the study period by a statistically significant amount, there was no "reduction" of 6MWD by more than 15% from a baseline value.

635. Because the results in Faria-Urbina 2018 show improvements that inversely relate to clinical worsening events (notably an increase in six-minute walk distance rather than a decrease) a POSA would have a reasonable expectation of success in seeing a statistically significant reduction in clinical worsening events when treating a patient with PH-ILD using the dosing regimens in Faria-Urbina 2018. (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937.) Moreover, claim 8 of the '327 patent defines "clinical worsening" as: "*at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.*" Therefore, the prior art does not also need to include reductions of hospitalizations for cardiopulmonary indication to meet the limitations of claim 8; demonstrating avoidance of a significant decline in 6MWD is sufficient.

636. UTC may argue that, despite Faria-Urbina 2018 and its Supplement reporting a statistically significant increase in 6MWD in the overall patient population, as well as the CPFE

population, there can still be improvement in the 6MWD for some patients and others who have deterioration in this parameter to meet this 15% reduction threshold. But Faria-Urbina 2018 notes that “[d]ata are presented as mean±standard deviation or as absolute numbers, unless otherwise stated.” (DTX0348, Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at UTC\_PH-ILD\_009938.) The percent increase for the average 6MWD (238 meters at baseline; 293 meters at three-month follow-up) yields a 23% increase in 6MWD. The percent increase for the lower bound 6MWD (229 meters at baseline; 273 meters at three-month follow-up) yields an 18% increase. And the percent increase for the upper bound 6MWD (247 meters at baseline and 315 meters at three-month follow-up) yields a 27.5% increase. None of the CPFE patients falling within the average, upper bound, or lower bound 6MWD data set experienced a deterioration in this parameter to meet this 15% reduction threshold.

637. Because the ’793 patent discloses the same drug, administered by the same route of administration, using the same dosing scheme to Faria-Urbina 2018, in a PH-ILD population, a POSA would have been motivated to combine Faria-Urbina 2018 with the ’793 patent to further evaluate a reduction in clinical worsening events and have a reasonable expectation of success given the results disclosed in Faria-Urbina 2018. Accordingly, claims 7 and 8 are invalid as obvious.

**e. Dependent Claims 9-10**

638. Asserted claim 9 requires that “said administering provides a statistically significant improves [sic] of forced vital capacity (FVC) in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.” Claim 10 requires that “said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.” A POSA would have been motivated to combine the teachings of Faria-Urbina

2018 with the '793 patent and Saggar 2014 to arrive at claims 9 and 10 and would have had a reasonable expectation of success in combining these teachings.

639. With respect to the improvement in FVC, 20 mL of lung volume is approximately 1–2 % of lung volume. Saggar 2014 reports an improvement of % predicted FVC in the treated patient population compared to baseline. Table 2 shows a change in % predicted FVC from 62% at baseline to 63% at 12 weeks. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000228 (Table 2).)

640. The '327 patent does not disclose a statistically significant p-value for improvements of FVC within the treatment group compared to baseline, but instead for the difference between FVC in the treated versus placebo patient population. ('327 patent at Tables 1, 2, and 3.) Moreover, the '327 patent discloses the % FVC change from baseline with subsets of the PH-ILD population including ITT, IIP, and IPF groups. (*Id.*) The % FVC change for these patient populations did not exceed a 1-2% increase in % predicted FVC compared to baseline. (*Id.*) For example, the % FVC change over baseline at week 8 for the ITT population was 0.77% and 1.07% at week 16 for the ITT population in the '327 patent. ('327 patent at Table 1.) Table 2 shows a 0.92% and 1.66% change in FVC over baseline at week 8 and week 16, respectively, for the IIP population and Table 3 shows a 1.60% and 1.62% change in FVC over baseline at week 8 and week 16, respectively, for the IPF population. (*Id.*) Additionally, the post-hoc analysis of the FVC data from INCREASE shows that a large percentage of patients in the trial actually had worse FVC after 16 weeks of treatment (46% got worse in for ITT; 40% for IIP, 39% for IPF, 47% for CPFE, and 53% for CTD). (DTX0404, 2021 Lancet Supplement (UTC\_PH-ILD\_112161) at UTC\_PH-ILD\_112168-169.)<sup>7</sup>

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<sup>7</sup> Figures 4a-d are labeled “at week 6” whereas Figure 3 says “at week 16.” Because the y axis of the Figure 4 histograms is still labeled “at week 16” it is likely that week 6 is a typo.

641. This magnitude of improvement is entirely consistent with the improvements seen in Saggar 2014 which reports a 1% improvement in % predicted FVC. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000228.) A POSA would expect to achieve a 1% change in FVC based on Saggar 2014. This is the value achieved and disclosed in the '327 patent, making it obvious in light of the Saggar 2014 disclosure.

642. For the reasons discussed above, a POSA would have been motivated to combine Saggar 2014 with Faria-Urbina 2018 and the '793 patent and have a reasonable expectation of achieving the results observed in Saggar 2014 since all three publications describe the use of treprostinil to treat PH, including PH-ILD. Therefore, claims 9 and 10 of the '327 patent are obvious.

**f. Dependent Claims 11 and 14**

643. Claim 11 is directed at “[t]he method of claim 1, wherein said administering is performed by a pulsed inhalation device.” ('327 patent at Claim 11.) Claim 14 then specifies, “[t]he method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising treprostinil or a pharmaceutically acceptable salt thereof.” (*Id.* at Claim 14.)

644. As discussed in paragraph 486, Faria-Urbina 2018 administered treprostinil by inhalation using the Tyvaso pulsed inhalation device, thus disclosing the limitation of claim 11.

645. The '793 patent also discloses the use of inhaled treprostinil via a pulsed inhalation device, thereby meeting the limitation of claim 11. Claim 3 of the '793 patent discloses the use of a pulsed ultrasonic nebulizer and claim 4 discloses the use of a dry powder inhaler. ('793 patent at Claims 3, 4.)

646. Claim 6 of the '793 recites “wherein the formulation is a powder” and claim 7 discloses “wherein the powder comprises particles less than 5 micrometers in diameter.” (*Id.* at Claims 6-7.)

647. The specification of the '793 patent describes inhalation devices for administering treprostinil including pulsed nebulizers (*id.* at 12:39-41, 14:35-41, 16:23-25) and a dry powder inhaler (*id.* at 12:39-41.). Example 2 of the '793 patent states that “TRE was inhaled with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler.” (*Id.* at 12:39-41.) It further describes that aerosol of treprostinil “was generated by a pulsed ultrasonic nebulizer (OPTINEB®, Nebutec, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause” and that “[t]he device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage.” (*Id.* at 14:36-42.) Claim 4 of the '793 patent recites “wherein the inhalation device is a dry powder inhaler[,]” while the specification further describes that “[t]he inhalation device can be also a dry powder inhaler” and “[i]n such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.” (*Id.* at Claim 4, 7:22-26.)

648. A POSA would be motivated to replace the nebulized solution used in Faria-Urbina 2018 with the dry powder inhaler disclosed in the '793 patent because dry powder inhalers are smaller and more convenient than nebulizers. In particular, the Optineb nebulizer used with the Tyvaso system utilized in Faria-Urbina 2018, and disclosed in the '793 patent, is a medium sized device that requires a carrying case. In contrast, a dry powder inhaler is a small, palm-sized device that employs capsules or small cartridges of dry powder formulations of drugs that are much more convenient to use and carry around. Thus, POSA would have been motivated to replace the nebulizer from Faria-Urbina 2018 with the dry powder inhaler of the '793 patent.

649. A POSA would have a reasonable expectation of making this switch based on the teachings of the '793 patent. Specifically, all of the examples of the '793 patent were conducted



using a nebulized solution of treprostinil and a pulsed inhalation device. But claims 4 and 6 of the '793 patent are directed to a dry powder inhaler and a dry powder formulation of treprostinil. Thus, based on data obtained using a nebulized solution of treprostinil and a nebulized pulsed inhalation device, the inventors still claimed a dry powder inhaler and formulation. Accordingly, a POSA, based on the '793 patent disclosure and claims, would have a reasonable expectation of successfully replacing the device from Faria-Urbina 2018 with a dry powder inhaler of the '793 patent, rendering claim 14 obvious.

650. A POSA does not need to believe that a dry powder inhaler is interchangeable with a nebulizer but merely needs motivation and a reasonable expectation of success to use it. Thus, a POSA would have a reasonable expectation of success when replacing the nebulizer used in Faria-Urbina 2018 with a dry powder inhaler and dry powder formulation of treprostinil, rendering claim 14 obvious.

**g. Dependent Claim 15**

651. Claim 15 is directed to a “method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg.” ('327 patent at Claim 15.)

652. Faria-Urbina 2018 alone discloses claim 15. Faria-Urbina 2018 describes administration of inhaled treprostinil “three breaths (18 µg) four times daily (72 µg/day),” which can be “increased as tolerated by three additional breaths (18 µg) per dosing session every 3-7 days to achieve a dose of at least 9-12 breaths or more ( $\geq 54$  µg) four times daily.” (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937.)

653. Because Faria-Urbina 2018 describes “a single inhalation administration event” ranging from 18µg to 72 µg, a POSA would understand that this range falls within “15 µg to 100 µg” and, thus, meeting the limitation of claim 15.

654. A POSA would also understand that the '793 patent discloses claim 15 based on its specification. A POSA would first understand that the “single event dose” disclosed by the '793 patent is equivalent to a “single inhalation administration” because both phrases refer to a single instance of administering inhaled treprostinil. ('327 patent at 21:20-48.) From the specification, a POSA would have understood that 15 µg to about 100 µg in preferably 3, 2, or 1 breaths would be anywhere from 5 µg to 100 µg per breath (i.e., 15 µg/3 breaths to 100 µg/1 breath), which discloses claim 15. ('793 patent at 7:55-59, 7:60-64.)

655. To the extent UTC disputes that Faria-Urbina 2018 anticipates claim 15, a POSA would have been motivated to combine the teachings of the '793 patent with Faria-Urbina 2018 to arrive at claim 15 and would have had a reasonable expectation of success in combining these teachings because the '793 patent and Faria-Urbina 2018 describe the use of treprostinil to treat PH, including PH-ILD.

#### **h. Dependent Claim 16**

656. Claim 16 is directed to a “method of claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient.” ('327 patent at Claim 16.)

657. Faria-Urbina 2018 alone discloses claim 16. Faria-Urbina 2018 describes a dose that can be “increased as tolerated by three additional breaths (18 µg) per dosing session every 3-7 days to achieve a dose of at least 9-12 breaths or more (~54 µg) four times daily.” (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937.) Faria-Urbina 2018 also disclosed that 18 of 22 patients achieved a target dose of greater than 216 µg and that the mean final dose for the entire cohort was 274 µg per day. A target dose of 216 µg per day results in 54 µg per single administration event, which is 9 breaths at 6 µg per breath. At the mean final dose of 274 µg, this would equate to approximately 68.5 µg per single administration event, which is approximately

12 breaths per single administration event. Patients in Faria-Urbina 2018, therefore, had single inhalation administration events that did not exceed 15 breaths, anticipating claim 16.

658. The '793 patent also discloses claim 16. The '793 patent discloses that administering treprostinil in a single event can occur “in 20 breaths or less, or in 10 breaths or less, or than 5 breaths or less” thereby anticipating claim 16. ('793 patent at 7:60-64.) It goes on to disclose that treprostinil is preferably administered in 3, 2, or 1 breaths, which do not exceed the 15 breaths limitation covered by claim 16. (*Id.*)

659. To the extent UTC disputes that Faria-Urbina 2018 anticipates claim 16, a POSA would have been motivated to combine the teachings of the '793 patent with Faria-Urbina 2018 to arrive at claim 16 and would have a reasonable expectation of success because both references describe the use of treprostinil to treat PH, including PH-ILD and similar dosing regimens that do not go beyond 15 breaths by the patient in a single administration event.

**i. Dependent Claims 17-19**

660. Claims 17–19 are directed to various improvements in 6MWD. Claim 17 requires an increase in 6MWD “by at least 10 m after 8 weeks of the administering,” claim 18 requires an improvement “by at least 15 m after 12 weeks of the administering,” and claim 19 requires an improvement “by at least 15 m after 16 weeks of the administering.” ('327 patent at Claims 17–19.)

661. As discussed in paragraphs 489-491, Faria-Urbina 2018 alone discloses claims 17-19.

662. UTC may assert that Faria-Urbina 2018 does not disclose claims 17-19 because that fact that the patients were “followed for at least 3 months” does not satisfy these claims’ requirement for testing 8, 12, or 16 weeks after administration. UTC substitutes the word “after” with the word “at,” contending that the 6MWD result claimed in claims 17, 18, and 19 must occur

“at the 8 [or 12 or 16] week mark.” Because Faria-Urbina 2018 provides data for week 12, which is after both weeks 8 and 12, it anticipates claims 17-18. Even if claims 18 and 19 would include both “after” and “at,” the Faria-Urbina 2018 3-month data still meets this limitation because a statistically significant change of at least 65 meters occurred at the 12-week mark, indicating that any improvement in 6MWD after the 12-week mark would likely be greater than 65 meters. This would safely encompass the “by at least 15 m after 16 weeks” limitation of claim 19.

663. Because the ’793 patent discloses the same drug, administered by the same route of administration, using the same dosing scheme to Faria-Urbina 2018, and in a PH-ILD population, a POSA would have been motivated to combine Faria-Urbina 2018 with the ’793 patent to further evaluate inhaled treprostinil’s impact on 6MWD in PH-ILD patients and have a reasonable expectation of successfully obtaining the results disclosed in Faria-Urbina 2018 and claimed in claims 17-19. (Anticipated testimony of Dr. Channick.)

**C. Claims 1-11 and 14-19 of the ’327 Patent Are Obvious Over Agarwal 2015 in Combination with the ’793 Patent and Saggat 2014**

**1. A POSA Would Have Been Motivated to Combine Agarwal 2015 with the ’793 Patent and Saggat 2014**

664. A POSA would have been motivated to combine the teachings of Agarwal 2015 with the ’793 patent and would have had a reasonable expectation of success in combining these teachings. As an initial matter, both references describe treating Group 3 PH patients, including PH-ILD patients, with inhaled treprostinil according to similar, if not identical, dosing schemes (i.e., between 15 and 90 µg in 3 breaths with a nebulizer and administered several times per day). (DTX0137, Agarwal 2015 at LIQ\_PH-ILD\_00147321; *see* Waxman Depo. Tr. at 57:10-59:12; *see also* ’793 patent at 7:55-64.)

665. Agarwal 2015 discloses treating PH-ILD to improve exercise capacity using inhaled treprostinil and the standard dosing from the Tyvaso® label as of 2009, motivating a POSA

to use Agarwal 2015 in the same manner as the reference discloses. (*See* paragraphs 160-164, *see also* 508-534.)

666. The '793 patent discloses and claims the use of inhaled treprostinil, the treatment of patients with PH-ILD, and hemodynamic results. (*See* paragraphs 187-203, 595-663.)

667. The '793 patent also teaches the advantages of inhaled treprostinil over other systemic vasodilators as the delivery method would not worsen V/Q mismatch. This, and its description of inhaled treprostinil as having “excellent tolerability at doses” and “well tolerated in concentrations up to 2000 mg/ml” and “in high doses (up to 90 micrograms)” would motivate a POSA to at least select inhaled treprostinil over other vasodilators and how to start prescribing the dose that should be used in PH-ILD patients. (*See* paragraph 563.) Thus, a POSA would be motivated to use the '793 patent in the same manner it discloses.

668. A POSA using inhaled treprostinil to treat PH-ILD according to Agarwal 2015 and the '793 patent would reasonably expect to treat PH-ILD patients and improve their exercise capacity, as well as other parameters, because that is exactly what Agarwal 2015 achieved, and one would expect based on the positive hemodynamic impact reported in Table 3 of the '793 patent in the studied patient population, including PH-ILD. Based on the disclosures of these references, a POSA would have been motivated to combine Agarwal 2015 and the '793 because of the similar subject matter.

669. Accordingly, a POSA would have been motivated to combine Agarwal 2015 with the '793 patent.

**a. The State of the Art and the Knowledge of a POSA before 2020 Also Motivates a POSA to Combine Agarwal 2015 with the '793 Patent**

670. A POSA would have been motivated to combine Agarwal 2015 with the '793 patent based on the state of the art prior to 2020, including at least U.S. Patent App Publication No.

2013/0096200 A1 (“Wade 200”) and Parikh 2016, as well as the knowledge of a POSA at this time.

671. To the extent UTC contends that a POSA would not be motivated to use inhaled treprostinil to treat PH-ILD, their own Wade 200 published application proves otherwise. The disclosure of Wade 200 is provided in paragraphs 144-149. Moreover, UTC and its experts cannot state that a POSA would lack an expectation of success in treating PH-ILD with inhaled treprostinil. UTC filed a patent application in 2013 that expressly discloses the use of inhaled treprostinil to treat PH-ILD. (DTX0361, Wade 200 at Claims 1-2, [0012], [0020]; *see also* Wade Depo. Tr. at 32:14-33:17.) Thus, UTC’s own patent application, Wade 200, also provides a POSA with a motivation and reasonable expectation of improving exercise capacity in patients with PH-ILD using inhaled treprostinil.

672. In addition to Wade 200, Parikh 2016 expressly discloses the use of inhaled treprostinil to treat PH-ILD patients as discussed in paragraphs 165-168. Parikh 2016 also reflected UTC’s knowledge of off-label use of Tyvaso in PH-ILD patients. (Smith Depo. Tr. at 78:24-79:10.) Thus, the successful results disclosed in Parikh 2016 provide a POSA with a reasonable expectation of successfully treating PH-ILD with inhaled treprostinil.

**b. The INCREASE Study and statements from UTC Confirm that a POSA Would Have been Motivated to Combine Agarwal 2015 with the ’793 Patent**

673. The INCREASE Study and statements from UTC discussed in Section V.D further confirm that a POSA would be motivated to combine Agarwal 2015 with the ’793 patent. The NEJM Publication, INCREASE Study Protocols, and Investigator Brochure, discussed in paragraphs 569-576 all directly reference Agarwal 2015 as motivation to use inhaled treprostinil to treat PH-ILD, and provide a reasonable expectation that such administration will be successful.

674. For example, the “Rationale For Development of Study Drug in Disease/Condition” section of the INCREASE Study protocols specifically reference Agarwal 2015 as motivation, stating:

Finally, Agarwal and colleagues (Agarwal 2015) recently presented data on 35 patients with WHO Group 3 PH who received treatment with inhaled treprostinil for six months. This retrospective review reported a mean increase from baseline in 6MWD of 61 meters with obstructive and restrictive patients reporting mean increases of 71 meters and 50 meters, respectively. Notably, this study also found that inhaled treprostinil was well tolerated with cough being the most commonly reported AE. Data from these recently completed pilot studies ***suggest that inhaled treprostinil can be safely administered in patients with WHO Group 3 PH.***

(DTX0373, Original Protocol at UTC\_PH-ILD\_054899-900; DTX0401, Final Protocol at UTC\_PH-ILD\_065990-991 (emphasis added).)

Thus, based on prior art disclosures, UTC acknowledged not only a motivation to use inhaled treprostinil to treat PH-ILD, but a reasonable expectation that such administration will be successful.

675. Furthermore, as discussed in paragraphs 575 above, Dr. Rothblatt’s statement that “[t]his drug works” and that she has seen “posters” and “papers” on this issue reflects acknowledgment that references prior to April 2020 speak directly to the study of Tyvaso in PH-ILD patients. Thus, based on these disclosures, UTC’s own publications establish that a POSA would have been motivated to combine Agarwal 2015 with the ’793 patent and Saggar 2014 to improve the exercise capacity of PH-ILD patients using inhaled treprostinil.

**c. Non-Confidential Presentations Concerning Faria-Urbina 2018 as “Preliminary” and “Supportive Evidence” Confirm that a POSA Would Have Been Motivated to Combine Agarwal 2015 and the ’793 Patent**

676. The non-confidential information from the public presentations discussed in paragraphs 577-583 further confirm that a POSA would be motivated to combine Agarwal 2015

with the '793 patent. The 2017 Recruitment Presentation, 2017 John Vane Presentation, and 2018 Waxman Presentation all served as motivation to use inhaled treprostinil to treat PH-ILD and provide a reasonable expectation that such administration will be successful. While these presentations concerned Faria-Urbina 2018, Dr. Waxman confirmed that the patients included in Agarwal 2015 were also part of Faria-Urbina 2018. (Waxman Depo. Tr. at 30:10-31:16.) Thus, based on these disclosures, UTC acknowledged not only a motivation to use inhaled treprostinil to treat PH-ILD, but a reasonable expectation that such administration will be successful.

**d. A POSA Would Have a Reasonable Expectation of Successfully Combining Agarwal 2015 with the '793 Patent to Improve the Exercise Capacity of Patients with PH-ILD**

677. Based on the disclosures of Agarwal 2015, the '793 patent, the fact that physicians were already treating PH-ILD patients with inhaled treprostinil and seeing improvements in their exercise capacity, and that UTC believed treating PH-ILD patients with inhaled treprostinil would be successful, a POSA would have had a reasonable expectation of successfully improving the exercise capacity of PH-ILD patients by administering inhaled treprostinil.

678. The fact that Agarwal 2015, as discussed above in paragraphs 160-164, actually treated PH-ILD patients with Tyvaso® and saw positive results in a number of parameters, including the 6MWD test, would not only motivate a POSA to use Agarwal 2015, but the actual positive results provide a POSA with a reasonable expectation of success.

679. Additionally, the '793 patent would also give a POSA a reasonable expectation of success. As discussed in paragraph 193, above, UTC told the FDA and the PTO that the '793 patent claims cover the FDA approved PH-ILD indication. Again, that acknowledgement by UTC not only demonstrates a reasonable expectation of success based on the '793 patent, but actual success, as physicians prescribed Tyvaso® to PH-ILD patients prior to 2020 and did so according to the Tyvaso® label, covered by the claims of the '793 patent.



**e. A POSA Would have a Reasonable Expectation of Success of Combining Agarwal 2015 with the '793 Patent Based on Doctor's Use of Tyvaso to Treat PH-ILD Prior to 2020**

680. As discussed in paragraphs 107-141, POSAs were already administering PH-ILD patients with inhaled treprostinil long before April 2020. As evidenced by the positive studies discussed above, many physicians measured hemodynamics in these patients and also measured and saw significant improvements in exercise capacity. (Rajeev Saggar Depo. Tr. at 222:13-223:12; Rajan Saggar Sept. 17, 2024 Depo. Tr. at 20:17-21:18; Tapson Depo. Tr. at 40:5-21; Waxman Depo. Tr. at 204:24-205:5; DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508; DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009936.) The testimony of these clinicians from their real world practices again provide not only a reasonable expectation of success in using inhaled treprostinil to treat PH-ILD patients, but proof of actual success.

**2. Claim 1 of the '327 Patent is Obvious Over Agarwal 2015 in Combination with the '793 Patent**

681. A POSA would have been motivated to combine the teachings of Agarwal 2015 with the '793 patent to arrive at the limitations of claim 1[a]-[d] and would have had a reasonable expectation of success in combining these teachings.

682. As discussed in paragraphs 160-164 and 508-517 above, a POSA would have understood that Agarwal 2015 discloses a method of improving exercise capacity in a patient having PH associated with interstitial lung disease. Agarwal also discloses claim limitations 1[b]-1[d]. Agarwal 2015 describes "Group-3 PH" patients, including 15 with restrictive diseases, as "receiving inhaled Treprostinil (iTre)[,]" where doses started at "3-breaths (br) 4X daily and increased to a goal of 9-12 br 4x daily as tolerated." (DTX0344, Agarwal 2015 at UTC\_PH-ILD\_009828 (Purpose, Methods).) Dr. Waxman confirmed that Agarwal 2015 used the standard Tyvaso® dosing. (Waxman Depo. Tr. at 57:10-59:12.) Based on the state of the art in 2015

(including the Tyvaso® Label and the fact that physicians including myself regularly dosed patients with 3-breaths 4X daily to a goal of 9-12 breaths as tolerated), a POSA would have expected that “3-breaths (br) 4X daily” refers to the known dosing regimen for Tyvaso®, which in 2015 started at 3 breaths 4 times daily with approximately 6 mcg of treprostinil per breath.

683. As discussed in paragraphs 598 and 603-604, the '793 patent also independently meets the limitations of claim 1[a]-[d].

684. Because both references independently disclose all of claim 1, a POSA would have been motivated to combine Agarwal 2015, with the '793 patent's method of treatment to arrive at claim 1 of the '327 patent. Specifically, Agarwal 2015 achieved the results disclosed in PH-ILD patients by treating them with inhaled treprostinil identical to the dosing scheme disclosed and claimed in the '793 patent (i.e., between 15 and 90 µg in 3 breaths administered several times per day). Because the results in Agarwal 2015 demonstrated improvements in exercise capacity, a POSA would have had a reasonable expectation of success when combining Agarwal 2015 with the '793 patent.

**3. Dependent Claims 2-11 and 14-19 of the '327 Patent Are Obvious Over Agarwal 2015 in Combination with the '793 Patent and Saggat 2014**

**a. Dependent Claims 2-3**

685. Dependent claim 2 requires a “statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks” and claim 3 requires an increase in 6MWD “by at least 10 m after 8 weeks, 12 weeks, or 16 weeks” of administering inhaled treprostinil. The combination of Agarwal 2015 with the '793 patent renders claims 2-3 obvious.

686. Agarwal 2015 reports that the mean change in 6MWD as “+60.85m +/- 92.60” with a p value of 0.0019, which demonstrated a statistically significant improvement. (DTX0344, Agarwal 2015 at UTC\_PH-ILD\_009828 (Results); Waxman Depo. Tr. at 63:22-64:13.) Agarwal

2015 further reports an improvement of  $50\text{m} \pm 57$  (median +61m) in 6MWD in patients with “restrictive disease” (i.e., PH-ILD). (DTX0344, Agarwal 2015 at UTC\_PH-ILD\_009828 (Results).) Agarwal 2015 further reports an improvement of  $50\text{m} \pm 57$  (median +61m) in 6MWD in patients with “restrictive disease” (i.e., PH-ILD). (DTX0344, Agarwal 2015 at UTC\_PH-ILD\_009828 (Results).) Because Agarwal 2015 discloses a statistically significant improvement in 6MWD and reports that the patients had an average increase of 60m in their 6MWD after 6 months, it meets the limitations of claims 2 and 3.

687. UTC may contend that Agarwal does not meet the limitations of claims 2-3 because it includes a non-homogenous population of Group 3 PH patients. However, as mentioned in paragraph 16, patients with “restrictive disease” are PH-ILD patients. (Anticipated testimony of Dr. Channick; *see also* ’793 patent at 17:59-18:5 (stating interstitial lung disease is a type of restrictive disease.) Claim 1 only states that the patient population includes “a patient having pulmonary hypertension associated with interstitial lung disease,” *i.e.*, PH-ILD patients. (’327 patent at Claim 1.) Accordingly, the 6MWD results of PH-ILD patients within the Faria-Urbina 2018 patient population also meet the limitations of claims 2 and 3.

688. Because the ’793 patent discloses the same drug, administered by the same route of administration, using the same dosing scheme to Agarwal 2015, and in a PH-ILD population, a POSA would have been motivated to combine Agarwal 2015 with the ’793 patent to further evaluate inhaled treprostinil’s impact on 6MWD in PH-ILD patients. Specifically, Table 3 of the ’793 patent discloses that 15 pulmonary fibrosis patients (i.e. PH-ILD patients) were part of the study. (’793 patent at Table 3 (Etiology of pulmonary hypertension where pulmonary fibrosis is category (f)).) The ’793 patent also discloses positive hemodynamic results (treprostinil inhalation led to “maximal decreases of PVR to  $76.5 \pm 4.7\%$  (30  $\mu\text{g}$ ),  $73.7 \pm 5.8\%$  (60  $\mu\text{g}$ ),  $73.3 \pm 4.3\%$  (90  $\mu\text{g}$ )

and  $65.4 \pm 4.1\%$  ( $120 \mu\text{g}$ ) of baseline values” and “[c]ardiac output was increased to a maximum of  $106.8 \pm 3.2\%$  ( $30 \mu\text{g}$ ),  $122.9 \pm 4.3\%$  ( $60 \mu\text{g}$ ),  $114.3 \pm 4.8\%$  ( $90 \mu\text{g}$ ) and  $111.3 \pm 3.9\%$  ( $120 \mu\text{g TRE}$ ).”) which correlate to an improvement in exercise capacity. (*Id.* at 15:48-60, Figs. 8, 9; anticipated testimony of Dr. Channick.) Therefore, a POSA reading the ’793 patent would have a reasonable expectation of success in combining Agarwal 2015 with the ’793 patent and treating PH-ILD patients with inhaled treprostinil in order to achieve the 6MWD results required by claims 2 and 3.

**b. Dependent Claims 4-5**

689. Claims 4 and 5 disclose “[t]he method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering[.]” and “[t]he method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering[.]” respectively. (’327 patent at Claims 4-5.) A POSA would have been motivated to combine the teachings of Agarwal 2015 and the ’793 patent with Saggar 2014 to arrive at the limitations in claims 4 and 5 and would have had a reasonable expectation of success in doing so.

690. A POSA would have been further motivated to combine Saggar 2014, with Agarwal 2015 and the ’793 patent because Saggar 2014 discloses the use of treprostinil to treat PH, including PH-ILD, and because it discloses additional measurements relevant to in the safe and effective treatment of PH-ILD patients. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000226-228.) A POSA would be motivated to replace the parenteral treprostinil used in Saggar 2014 with inhaled treprostinil disclosed in Agarwal 2015 and the ’793 patent in order to minimize or avoid the issue of V/Q mismatch. (Anticipated testimony of Dr. Channick.)

691. In Saggar 2014, patients treated with parenteral treprostinil saw their BNP (brain natriuretic peptide) levels fall from 558 pg/ml to 228 pg/ml, a difference of 330 pg/ml, after 12 weeks and a p-value of 0.004. (DTX0010, Saggar 2014 at LIQ-PH-ILD\_00000230 (Table 4).) As explained above in paragraphs 155 and 611-616, there is a positive correlation between BNP and NT-proBNP and they are typically viewed as being congruent. Further, because positive results in 6MWD and hemodynamics were observed in PH-ILD patients in both parenteral and inhaled routes of treprostinil administration, a POSA would reasonably expect to achieve a statistically significant reduction in NT-proBNP as well as a reduction of at least 200 pg/ml after 8, 12 or 16 week of the administration as observed in Saggar 2014, when administering treprostinil via inhalation as in Agarwal 2015 and the '793 patent. (Anticipated testimony of Dr. Channick.)

692. Furthermore, Wade 200 correlates parenteral treprostinil with inhaled treprostinil. Wade 200 discloses both parenteral treprostinil and inhaled treprostinil in the context of treating PH-ILD and that an effective dose would be between 5-500 mcg “inhaled treprostinil per day.” (DTX0361, Wade 200 at [0013].) Wade 200 also measure BNP and it expressly discloses that “[s]ubjects receiving Treprostinil *will show improvements* in the studied criteria . . . .” (DTX0361, Wade 200 at [0082]-[0087] (emphasis added).) UTC, via Wade 200, is stating that all of these measured endpoints will improve using treprostinil. Wade 200 thus motivates one to combine Agarwal 2015, with the '793 patent and Saggar 2014 with an expectation of success.

693. Additionally, a statistically significant improvement would have been obvious given the state of the art. Statistical significance is merely a matter of adequately powering a study with a sufficient number of patients, reflecting study design and sample size. The '327 patent did not identify a novel therapeutic effect but merely replicated what was already known in Agarwal 2015 by evaluating the same drug, administered by the same route of administration, using the

same dosing, in the same PH-ILD population. (Anticipated testimony of Dr. Channick.) The '327 patent simply studied more PH-ILD patients than Agarwal 2015. Given that statistical significance is a matter of mathematical power, and physicians were seeing benefits in treating PH-ILD patients with inhaled treprostinil, a statistically significant change in any metric is obvious in light of the prior art.

694. Thus, the combination of Agarwal 2015, the '793 patent and Saggar 2014 renders claims 4 and 5 obvious.

695. UTC may contend that a POSA would not be able to predict how changing both the dosage and administration route for treprostinil would affect the results described in Saggar 2014 and in view of Saggar 2014's small sample size and lack of control arm. However, the sample size is not disqualifying as prior art and a POSA would not simply disregard relevant clinical reports due to sample size. In fact, patient case studies and retrospective reviews are common and important sources of information and evidence in clinical practice. The clinical results seen in Saggar 2014 are actual results and therefore a POSA would consider them relevant to treating PH-ILD patients with inhaled treprostinil. The combination of Agarwal, the '793 patent, and Saggar 2014 and thus, claims 4-5 are still rendered obvious.

**c. Dependent Claim 6**

696. Claim 6 is directed to a "method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease." ('327 patent at Claim 6.)

697. As explained in paragraph 621 above, if a patient demonstrates a statistically significant improvement in functional class or 6MWD, a POSA would conclude that a statistically significant reduction in exacerbations to also occur. (Anticipated testimony of Dr. Channick.)

698. Agarwal 2015 discloses that patients showed an improvement in 6MWD while “30 [patents] had subjective improvement.” (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508.) It also discloses the mean change in 6MWD was 60.85 meters  $\pm$  92.60 meters with a p value of 0.0019. (*Id.*) Because Agarwal 2015 describes an overall benefit to the patients, a POSA would have expected that the patients also showed an improvement in PH-ILD exacerbations.

699. A statistically significant reduction in exacerbations would also have been obvious given the state of the art. Statistical significance is merely a matter of adequately powering a study with a sufficient number of patients, reflecting study design and sample size. The ’327 patent did not identify a novel therapeutic effect but merely replicated what was already known in Faria-Urbina 2018 by evaluating the same drug, administered by the same route of administration, using the same dosing, in the same PH-ILD population. (Anticipated testimony of Dr. Channick.) The ’327 patent simply studied more PH-ILD patients than Agarwal 2015.

700. Saggat 2014 also disclosed statistically significant improvements in 6MWD (mean 59 m;  $p < 0.001$ ), along with improvements in dyspnea, also known as shortness of breath, which were measured using the University of California San Diego Shortness of Breath (UCSD SOB) questionnaire and Short Form Health Survey (SF-36), respectively. (DTX0010, Saggat 2014 at LIQ\_PH-ILD\_00000228-229.) The patients’ UCSD SOB scores changed from 87 to 73.1 with a p value of 0.002, patients’ SF-36 MCS scores increased from 38 to 33.2 with a p-value of 0.005 indicating improvements in shortness of breath. (*Id.*)

701. An improvement in shortness of breath as well as an improvement in 6MWD, demonstrates that there is a reduction in respiratory deterioration due to alveolar abnormalities. (*See* Waxman Depo. Tr. at 116:3-18.) Thus, it would have been obvious to a POSA that

administration of treprostinil would result in a statistically significant reduction in at least one exacerbation of ILD.

702. While Saggat 2014 uses parenteral treprostinil, for the reasons discussed in paragraph 692, a POSA would have been motivated to combine its teachings with those of Agarwal 2018 and the '793 patent since all three publications describe the use of treprostinil to treat PH, including PH-ILD. A POSA would have a reasonable expectation of success because Agarwal 2015 and Saggat 2014 to reach a method resulting in a statistically significant reduction in exacerbations because both references report improvements in shortness of breath and improvements in 6MWD, a proxy for respiratory function and clinical status which suggests reductions in respiratory deterioration. (Anticipated testimony of Dr. Channick.)

703. Additionally, the similarities in patient population, drug, and observed clinical benefits would lead a POSA to expect that the inhaled formulation could achieve comparable outcomes. By combining the disclosures of these three references, a POSA would have had a reasonable expectation of success in achieving the limitation of asserted claim 6 of the '327 patent.

**d. Dependent Claims 7-8**

704. Claim 7 is directed to “[t]he method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease[]” and claim 8 is directed to “[t]he method of claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.” ('327 patent at Claims 7-8.)

705. The '327 patent specification defines “clinical worsening” as including “one or more of hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death or a lung transplantation.” ('327 patent at 19:57-60,



30:52-60.) Generally, when patients are feeling better, they probably are not experiencing clinical worsening. (Anticipated testimony of Dr. Channick; Rajan Saggar Sept. 17, 2024 Depo. Tr. at 163:3-15.)

706. Agarwal 2015 discloses improvements, including improvements in 6MWD, that inversely relate to clinical worsening events. Specifically, Agarwal 2015 reports that the mean change in 6MWD as “+60.85m +/- 92.60 (median change +45m,  $p = 0.0019$ ),” which demonstrates a statistically significant improvement. (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508.) Agarwal 2015 also reported that 24 patients experienced “subjective improvement” which also indicates that PH-ILD patients treated with inhaled treprostinil experience a reduction in clinical worsening. (*Id.*)

707. Based on the '327 patent's definition of “clinical worsening,” a POSA would understand that a statistically significant *increase* in 6MWD indicates a statistically significant reduction of a clinical worsening event involving 6MWD as required by claims 7 and 8. That is, because patients' 6MWD increased over the study period by a statistically significant amount, there was no “reduction” of 6MWD by more than 15% from a baseline value.

708. Because the results in Agarwal 2015 show improvements that inversely relate to clinical worsening events (notably an increase in six-minute walk distance rather than a decrease) a POSA would have a reasonable expectation of success in seeing a statistically significant reduction in clinical worsening events when treating a patient with PH-ILD using the dosing regimen in Agarwal 2015. (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508.) Moreover, claim 8 of the '327 patent defines “clinical worsening” as: “*at least one of* hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.” Therefore, the prior art

does not also need to include reductions of hospitalizations for cardiopulmonary indication to meet the limitations of claim 8; demonstrating avoidance of a significant decline in 6MWD is sufficient.

709. Because the '793 patent discloses the same drug, administered by the same route of administration, using the same dosing scheme to Agarwal 2015, in a PH-ILD population, a POSA would have been motivated to combine Agarwal with the '793 patent to further evaluate a reduction in clinical worsening events and have a reasonable expectation of success given the results disclosed in Agarwal 2015. Accordingly, claims 7 and 8 are invalid as obvious.

**e. Dependent Claims 9-10**

710. Claim 9 requires that "said administering provides a statistically significant improves [sic] of forced vital capacity (FVC) in the patient after 8 weeks, 12 weeks or 16 weeks of the administering." Claim 10 requires that "said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering." ('327 patent at Claims 9-10.) A POSA would have been motivated to combine the teachings of Agarwal 2015 with the '793 patent and Saggar 2014 to arrive at claims 9 and 10 and would have had a reasonable expectation of success in combining these teachings.

711. With respect to the improvement in FVC, 20 mL of lung volume is approximately 1–2 % of lung volume. Saggar 2014 reports an improvement of % predicted FVC in the treated patient population compared to baseline. Table 2 shows a change in % predicted FVC from 62% at baseline to 63% at 12 weeks. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000228 (Table 2).)

712. As discussed in paragraph 52-57 and 638-642 above, the '327 patent does not disclose a statistically significant p-value for improvements of FVC within the treatment group compared to baseline, but instead for the difference between FVC in the treated versus placebo patient population. ('327 patent at Tables 1, 2, and 3.) Moreover, the '327 patent discloses the %

FVC change from baseline with subsets of the PH-ILD population which do not exceed a 1-2% increase in % predicted FVC compared to baseline. (*Id.*)

713. This magnitude of improvement is entirely consistent with the improvements seen in Saggar 2014 which reports a 1% improvement in % predicted FVC. (DTX0010, Saggar 2014 at LIQ\_PH-ILD\_00000228.) A POSA would expect to achieve a 1% change in FVC based on Saggar 2014. This is the value achieved and disclosed in the '327 patent, making it obvious in light of the Saggar 2014 disclosure.

714. A POSA would have been motivated to combine Saggar 2014 with Agarwal 2015 and the '793 patent since all of these publications describe the use of treprostinil to treat PH, including PH-ILD. Moreover, a POSA would have had a reasonable expectation of success in achieving claims 9 and 10 of the '327 patent given the improvement in FVC reported in Saggar 2014 using treprostinil. Thus, the combination of Agarwal 2015 with the '793 patent and Saggar 2014 render claims 9-10 obvious.

**f. Dependent Claims 11 and 14**

715. Claim 11 is directed at “[t]he method of claim 1, wherein said administering is performed by a pulsed inhalation device.” ('327 patent at Claim 11.) Claim 14 then specifies, “[t]he method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising treprostinil or a pharmaceutically acceptable salt thereof.” (*Id.* at Claim 14.)

716. As discussed above, Agarwal 2015 administered treprostinil by inhalation using the Tyvaso® pulsed inhalation device, thus disclosing the limitation of claim 11.

717. As discussed in paragraphs 41, 187-203, and 645-47, the claims and the specification of the '793 patent also discloses the use of inhaled treprostinil via a pulsed inhalation device, thereby meeting the limitation of claim 11.

718. A POSA would be motivated to replace the nebulized solution used in Agarwal 2015 with the dry powder inhaler disclosed in the '793 patent because dry powder inhalers are smaller and more convenient than nebulizers. In particular, the Optineb nebulizer used with the Tyvaso system utilized in Agarwal 2015, and disclosed in the '793 patent, is a medium sized device that requires a carrying case. In contrast, a dry powder inhaler is a small, palm-sized device that employs capsules or small cartridges of dry powder formulations of drugs that are much more convenient to use and carry around. Thus, POSA would have been motivated to replace the nebulizer from Agarwal 2015 with the dry powder inhaler of the '793 patent.

719. A POSA would have a reasonable expectation of making this switch based on the teachings of the '793 patent. Specifically, all of the examples of the '793 patent were conducted using a nebulized solution of treprostinil and a pulsed inhalation device. But claims 4 and 6 of the '793 patent are directed to a dry powder inhaler and a dry powder formulation of treprostinil. Thus, based on data obtained using a nebulized solution of treprostinil and a nebulized pulsed inhalation device, the inventors still claimed a dry powder inhaler and formulation. Accordingly, a POSA, based on the '793 patent disclosure and claims, would have a reasonable expectation of successfully replacing the device from Agarwal 2015 with a dry powder inhaler of the '793 patent, rendering claim 14 obvious.

720. A POSA does not need to believe that a dry powder inhaler is interchangeable with a nebulizer but merely needs motivation and a reasonable expectation of success to use it. Thus, a POSA would have a reasonable expectation of success when replacing the nebulizer used in Agarwal 2015 with a dry powder inhaler and dry powder formulation of treprostinil, rendering claim 14 obvious.

**g. Dependent Claim 15**

721. Claim 15 is directed to a “method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15  $\mu$ g to 100  $\mu$ g.” (*Id.* at Claim 15.)

722. Agarwal 2015 discloses dosing regimens with 6, 9, 12, and 15 breaths per single inhalation administration event. (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508 (Methods).) Patients started out receiving 3 breaths of inhaled treprostinil 4 times daily and increased to 9-12 breaths 4 times daily, as tolerated. (*Id.* at LIQ\_PH-ILD\_00147321; *see* Waxman Depo. Tr. at 57:10-59:12.) Dr. Waxman confirmed that the Agarwal 2015 study was conducted using Tyvaso®, which was the only inhaled treprostinil product available as of 2015. (Waxman Depo. Tr. at 57:10-59:12.) This means each breath delivered 6 mcg, 3 breaths delivered 18 mcg per treatment session, and 4 treatment sessions per day delivered a total of 72 mcg per day. (DTX0357, 2009 Tyvaso® label at UTC\_PH-ILD\_010693 (“Dosing and Administration”); *see* Waxman Depo. Tr. at 57:10-59:12.) Because Agarwal 2015 discloses a dosing regimen with 6, 9, 12, and 15 breaths per single administration event, a POSA would understand that this dosing scheme would deliver an effective amount of treprostinil ranging from 18  $\mu$ g to 90  $\mu$ g per single inhalation administration event. (*See* DTX0357, 2009 Tyvaso® label at UTC\_PH-ILD\_010693 (“Dosing and Administration”) and UTC\_PH-ILD\_010703; *see* Waxman Depo. Tr. at 59:8-21.) A POSA would also understand that these amounts of inhaled treprostinil fall between 15  $\mu$ g and 100  $\mu$ g and thus the dosing regimen in Agarwal 2015 expressly teaches, and thus renders obvious, claim 15 of the ’327 patent.

723. A POSA would also understand that the ’793 patent discloses claim 15 based on its specification. A POSA would first understand that the “single event dose” disclosed by the ’793 patent is equivalent to a “single inhalation administration” because both phrases refer to a single

instance of administering inhaled treprostinil. ('327 patent at 21:20-48.) From the specification, a POSA would have understood that 15 µg to about 100 µg in preferably 3, 2, or 1 breaths would be anywhere from 5 µg to 100 µg per breath (i.e., 15 µg/3 breaths to 100 µg/1 breath), which discloses claim 15. ('793 patent at 7:55-59, 7:60-64.)

724. To the extent UTC disputes that Faria-Urbina 2018 anticipates claim 15, a POSA would have been motivated to combine the teachings of the '793 patent with Agarwal 2015 to arrive at claim 15 and would have had a reasonable expectation of success in combining these teachings because the '793 patent and Agarwal 2015 describe the use of treprostinil to treat PH, including PH-ILD.

#### **h. Dependent Claim 16**

725. Claim 16 is directed to a “method of claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient.” ('327 patent at Claim 16.)

726. Agarwal 2015 disclosed dosing regimens with 6, 9, 12, and 15 breaths per single inhalation administration event. (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508 (Methods).) Patients started out receiving 3 breaths of inhaled treprostinil 4 times daily and increased to 9-12 breaths 4 times daily, as tolerated. (*Id.* at LIQ\_PH-ILD\_00147321; *see* Waxman Depo. Tr. at 57:10-59:12.) Dr. Waxman confirmed that the Agarwal 2015 study was conducted using Tyvaso®, which was the only inhaled treprostinil product available as of 2015. (Waxman Depo. Tr. at 57:10-59:12.) This means each breath delivered 6 mcg, 3 breaths delivered 18 mcg per treatment session, and 4 treatment sessions per day delivered a total of 72 mcg per day. (DTX0357, 2009 Tyvaso® label at UTC\_PH-ILD\_010693 (“Dosing and Administration”); *see* Waxman Depo. Tr. at 57:10-59:12.) At 9 breaths, a patient would receive 54 mcg per treatment session for a total of 216 mcg per day (4 treatment sessions), and at 12 breaths, a patient would receive 72 mcg of treprostinil per treatment session and a total of 288 mcg of treprostinil per day

(4 treatment session). (See DTX0357, 2009 Tyvaso® label at UTC\_PH-ILD\_010693 (“Dosing and Administration”) and UTC\_PH-ILD\_010703; see Waxman Depo. Tr. at 59:8-21.) Only one patient was receiving 15 breaths per single administration event, and the single inhalation administration events never exceeded 15 breaths by the patient. Accordingly, a POSA would understand that Agarwal 2015 expressly meets, and thus renders obvious, claim 16 of the ’327 patent.

727. The ’793 patent also discloses Asserted Claim 16. The ’793 patent discloses that administering treprostinil in a single event can occur “in 20 breaths or less, or in 10 breaths or less, or than 5 breaths or less” thereby anticipating claim 16. (’793 patent at 7:60-64.) It goes on to disclose that treprostinil is preferably administered in 3, 2, or 1 breaths, which do not exceed the 15 breaths limitation covered by claim 16. (*Id.*)

728. Although Agarwal 2015 expressly meets the limitation of claim 16, a POSA would have been motivated to combine the teachings of the ’793 patent with Agarwal 2015 to arrive at claim 16 and would have a reasonable expectation of success because both references describe the use of treprostinil to treat PH, including PH-ILD, the same route of administration and similar dosing regimens that do not go beyond 15 breaths by the patient in a single administration event.

**i. Dependent Claims 17-19**

729. Claims 17–19 are directed to various improvements in 6MWD. Claim 17 requires an increase in 6MWD “by at least 10 m after 8 weeks of the administering,” claim 18 requires an improvement “by at least 15 m after 12 weeks of the administering,” and claim 19 requires an improvement “by at least 15 m after 16 weeks of the administering.” (’327 patent at Claims 17–19.)

730. Agarwal 2015 described treating 35 WHO Group-3 PH patients with inhaled treprostinil for 6 months. (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508 (Methods).) It

reports that the mean change in 6MWD as “+60.85m +/- 92.60” with a p value of 0.0019, which demonstrated a statistically significant improvement. (*Id.*; Waxman Depo. Tr. at 63:22-64:13.) Agarwal 2015 further reports an improvement of  $50\text{m} \pm 57$  (median +61m) in 6MWD in patients with “restrictive disease” (i.e., PH-ILD). (DTX0161, Agarwal 2015 at LIQ\_PH-ILD\_00148508 (Results).) This is greater than the “10 m increase *after* 8 weeks of the administering,” the “15 m after 12 weeks of administering,” and the “15 m after 16 weeks of administering,” described in claims 17-19 and thus meets the limitations of all three claims.

731. UTC may assert that Agarwal 2015 does not disclose claims 17-19 because that fact that the patients were treated for 6 months prevents Agarwal 2015 from satisfying these claims’ requirement for testing 8, 12, or 16 weeks after administration. UTC substitutes the word “after” with the word “at,” contending that the 6MWD result claimed in claims 17, 18, and 19 must occur “at the 8 [or 12 or 16] week mark.” Because Agarwal 2015 provides data after 8, 12, and 16 weeks, which is after both weeks 8 and 12, it meets the limitations of claims 17-19.

732. Because the ’793 patent discloses the same drug, administered by the same route of administration, using the same dosing scheme to Agarwal 2015, and in a PH-ILD population, a POSA would have been motivated to combine Agarwal 2015 with the ’793 patent to further evaluate inhaled treprostinil’s impact on 6MWD in PH-ILD patients. (Anticipated testimony of Dr. Channick). Specifically, Table 3 of the ’793 patent discloses that 15 pulmonary fibrosis patients (i.e. PH-ILD patients) were part of the study. (’793 patent at Table 3 (Etiology of pulmonary hypertension where pulmonary fibrosis is category (f)).) The ’793 patent also discloses positive hemodynamic results (treprostinil inhalation led to “maximal decreases of PVR to  $76.5 \pm 4.7\%$  (30  $\mu\text{g}$ ),  $73.7 \pm 5.8\%$  (60  $\mu\text{g}$ ),  $73.3 \pm 4.3\%$  (90  $\mu\text{g}$ ) and  $65.4 \pm 4.1\%$  (120  $\mu\text{g}$ ) of baseline values” and “[c]ardiac output was increased to a maximum of  $106.8 \pm 3.2\%$  (30  $\mu\text{g}$ ),  $122.9 \pm 4.3\%$



(60 µg), 114.3±4.8% (90 µg) and 111.3±3.9% (120 µg TRE).”) which correlate to an improvement in exercise capacity. (*Id.* at 15:48-60, Figs. 8, 9; anticipated testimony of Dr. Channick.) Therefore, a POSA reading the ’793 patent would have a reasonable expectation of success in combining Agarwal 2015 with the ’793 patent and treating PH-ILD patients with inhaled treprostinil in order to achieve the 6MWD results required by claims 17-19.

**D. Objective Indicia Do Not Support Non-Obviousness of Claims 1-11 and 14-19**

**1. The Results of the ’327 Patent are Not Unexpected**

733. The asserted claims of the ’327 patent are anticipated and obvious over the prior art. (Anticipated Testimony of Dr. Channick.) Physicians have been prescribing Tyvaso® off-label to treat PH-ILD patients since at least 2009. Thus, the ’327 patent merely confirmed what physicians already knew would happen when PH-ILD patients were administered inhaled treprostinil, thereby rendering the claims described in the ’327 patent not unexpected. (Anticipated Testimony of Dr. Channick.) Dr. Smith, a named inventor of the ’327 patent, confirmed as much when he testified that “[t]he INCREASE study, which used 9[µg] as the target dose, up to 12[µg], **confirmed** that Tyvaso was safe and effective in treating patients with PH-ILD.” (Smith Depo. Tr. at 233:7-10 (emphasis added).) Prior to 2020, UTC’s CEO publicly stated that physicians had seen “unmistakable signals” of treprostinil’s effectiveness in PH-ILD patients, physicians across the country regularly prescribed Tyvaso® off-label to PH-ILD patients, and concluding “This drug works.” (DTX0003, UTC 2018 Earnings Call at LIQ\_PH-ILD\_00000010.) Likewise, it was not unexpected that the claimed methods would result in increased 6MWD, improved FVC, and reductions in plasma concentrations of NT-proBNP, clinical worsening events, and exacerbations, because the prior art disclosed the use of treprostinil in PH-ILD patients using the claimed dosing regimen and achieving significant changes in these claimed parameters.

734. By at least 2009, physicians were already administering inhaled treprostinil to PH-ILD patients following the dosing instructions delineated in the 2009 Tyvaso® Label. (Anticipated Testimony of Dr. Channick.) As discussed in paragraphs 107-141 above, numerous doctors at different clinics across the country—including at least Drs. Rajan and Rajeev Saggar, Dr. Tapson, Dr. Waxman, Dr. Nathan, Dr. Parikh, Dr. Hill, and Dr. Channick—regularly prescribed inhaled treprostinil to PH-ILD patients off-label before 2020.

735. It is clear UTC knew that administering inhaled treprostinil to PH-ILD patients would improve exercise capacity long before filing the '327 patent. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (*Id.* at UTC\_PH-ILD\_082770.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (*Id.* at UTC\_PH-ILD\_082772.) UTC additionally requested and approved Dr. Waxman to submit a letter to the FDA stating in 2017 that, based on his prior clinical experience and publications, he “anticipated” that inhaled treprostinil would effectively treat PH-ILD. (DTX0280, P. Smith email re Dr. Waxman’s Orphan Drug Designation Letter to the FDA (November 15, 2017) (UTC\_LIQ00104554); *see also* DTX0281, Dr. A.

Waxman's letter re Orphan Drug Designation to the FDA (November 15, 2017) (UTC\_LIQ00104555).) The claimed results in the '327 patent cannot be "unexpected," when Dr. Waxman, with UTC's encouragement and approval, told the FDA in 2017 that based on his prior experience and published papers, this result would be "anticipated." (Anticipated Testimony of Dr. Channick.)

736. Dr. Waxman, moreover, gave a public presentation in 2017 at the 12th Annual John Vane Memorial Symposium where he stated that inhaled treprostinil works for the "vast majority" of PH-ILD patients and that "larger clinical trials" should be considered in these patients. (DTX0140, 2017 Waxman Tr. at LIQ\_PH-ILD\_00147342, LIQ\_PH-ILD\_00147344.) Thus, the '327 patent's claimed results were "expected," and that the '327 patent merely confirmed, with more patients, what was already known. (Anticipated Testimony of Dr. Channick.)

737. UTC may argue that Phase III clinical data or FDA approval would be required to render the claims of the '327 patent unexpected. However, the claims of the '327 patent do not require a Phase III clinical trial or FDA approval. (Anticipated Testimony of Dr. Channick.) That a Phase III trial needed for FDA approval was successful does not mean the claimed invention of the '327 patent was "unexpected," particularly here when everyone involved in the INCREASE study did not express doubt about its success. (Anticipated Testimony of Dr. Channick.) UTC's contention that a Phase III trial is needed and that the claims of the '327 patent disclose an unexpected result, is clearly contradicted by Dr. Martine Rothblatt's statement in 2018, prior to the conclusion of the INCREASE study, that "[t]his drug works." (DTX0003, 2018 UTC Earnings Call Transcript at LIQ\_PH-ILD\_00000010.) Furthermore, to the extent that UTC allegedly did not know they had a claimed method of treatment until the data was unblinded in February 2020,

is irrelevant as a POSA can still *expect* the claimed results even if he does not yet know those results with absolute certainty.

738. UTC may also argue that no doctors would have expected to successfully treat PH-ILD patients with a Group 1 PAH therapy. However, physicians regularly prescribed inhaled treprostinil to PH-ILD patients off-label prior to the '327 patent's filing date. (Anticipated Testimony of Dr. Channick.) Dr. Waxman also testified that it made sense for treprostinil which was approved in Group 1 PAH, to work in PH-ILD given the overlap in the two indications and the vasodilating action of treprostinil. (Waxman Depo. Tr. at 50:6-51:10.) And, by 2018, even UTC believed that Tyvaso® worked to improve exercise capacity in patients with PH-ILD. (DTX0003, 2018 UTC Earnings Call Transcript at LIQ\_PH-ILD\_00000010.)

739. Additionally, Dr. Rajan Saggar testified that he was not surprised by the results at all, as physicians were already seeing improvements in exercise capacity based on their own clinical practice:

Q: Given your -- your experience that we have talked about today, were you surprised that treatment of PH-ILD patients with TYVASO resulted in significant improvements in exercise capacity based on six-minute walk distance?

A: No.

Q: Why not?

A: I mean, we've already --we've already seen this in our own clinical practice.

(Rajan Saggar Depo. Tr. at 178:2-14 (objections omitted).)

740. UTC may point to what it calls "failed studies" to establish that the claims of the '327 patent were unexpected. (Anticipated testimony of Dr. Nathan.) However, none of these studies examined inhaled treprostinil in PH-ILD patients. (Anticipated testimony of Dr.

Channick.) Instead, these prior “failed” studies were conducted on drugs of different classes and/or were administered by different routes or in different diseases, as summarized in the chart below. For example, the only study conducted in PH-ILD patients (the ACTIVE Study) examined iloprost, not treprostinil, and the only study examining inhaled treprostinil (the PERFECT Study) was conducted in patients with PH-COPD, not PH-ILD. (*See also* Waxman Depo. Tr. at 47:23-48:15; *see also id.* at 48:3-6 (“Q. Why did you ever [sic; never] investigate Iloprost in Group-3? . . . A. We never found Iloprost to be effective. Q. In Group-3 or overall for the indication of -- A. Overall.”).) Moreover, both Dr. Nathan and Dr. Wertheim agree that for a different drug given by a different system, the results can be entirely different than what might be seen with another drug. (Anticipated testimony of Dr. Nathan and Dr. Wertheim.)

Study	Drug/Route	Disease
Iloprost (ACTIVE)	Inhaled iloprost	PH-IPF
STEP-IPF	Oral sildenafil	PH-IPF
BPHIT	Bosentan	PH-IIP
INSTAGE	Nintedanib + sildenafil	PH-IPF
RISE-IIP	Oral riociguat	PH-IIP
Sildenafil with Pirfenidone	Sildenafil + pirfenidone	PH-IPF
PERFECT	Inhaled treprostinil	PH-COPD
ARTEMIS-IPF	Ambrisentan	PH-IPF
BUILD 3	Bosentan	PH-IPF
MELODY-1	Macitentan	PH-LHD

741. And with respect to the PERFECT Study, a POSA would not expect PH-ILD patients to necessarily have the same reaction to inhaled treprostinil as PH-COPD patients. More importantly, UTC did not announce the termination of PERFECT study until September 20, 2022, and its results were not published until 2024. (DTX0365, UTC 8-K 2022 (UTC\_PH-ILD\_010839); DTX0604, Nathan et al., *Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results*, European Respiratory Journal (2024) (UTC-PH-

ILD\_227135), *available at* <https://pmc.ncbi.nlm.nih.gov/articles/PMC11154754/pdf/ERJ-00172-2024.pdf>.) Accordingly, a POSA *at the time of invention* in 2020-2021 would not have been aware of the “failed” PERFECT study and thus would not have been dissuaded from administering inhaled treprostinil to PH-COPD (much less PH-ILD) patients. In sum, these failed studies involving different drugs and/or different disease conditions would not have discouraged—and perhaps most importantly in fact did not discourage—POSAs from continuing the off-label use of Tyvaso® to treat PH-ILD. (Anticipated testimony of Dr. Channick.)

742. Finally, UTC criticizes the results of Saggar 2014, Agarwal 2015, and Faria-Urbina 2018 as merely “hypothesis-generating.” However, UTC ignores that even after the conclusion of the INCREASE study, Dr. Nathan and others characterized the FVC results in the INCREASE study as merely “hypothesis generating.” (DTX0009, Nathan 2021 (LIQ\_PH-ILD\_00000216) at LIQ\_PH-ILD\_00000224.) Specifically, the post-hoc analysis of FVC in the INCREASE study concluded that “inhaled treprostinil appears to have a salutary effect on loss of lung function in patients with ILD and associated pulmonary hypertension[,]” but noted that this finding was “hypothesis generating” and “warrants further validation in a prospective, randomised, placebo-controlled study.” (*Id.*) UTC nonetheless obtained patient claims in the ’327 patent directed to improvements in FVC. These facts run directly contrary to UTC’s argument that the “hypothesis generating” prior art results would not cause a POSA to expect the claimed results.

## **2. No Long-Felt but Unmet Need**

743. Given that the prior art disclosed the asserted claims of the ’327 patent and that physicians were already prescribing Tyvaso® to PH-ILD patients since at least 2009, the prior art and physicians had already solved any long-felt unmet need for the treatment of PH-ILD. (Anticipated Testimony of Dr. Channick.)

744. UTC has agreed that the need for treatments for pulmonary hypertension associated with interstitial lung disease was met before April 17, 2020. During the '793 patent IPR, UTC asserted that the '793 patent satisfies a long-felt unmet need by providing a treatment for pulmonary hypertension in patients with interstitial lung disease. Specifically, UTC asserted that “[t]he claimed invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension.” (DTX0007, Patent Owner Response at LIQ\_PH-ILD\_00000180.) UTC further characterized the invention in the '793 patent, stating that “[i]nhaled treprostinil is currently approved for pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease.” (*Id.*)

745. UTC’s expert, Dr. Waxman, submitted a declaration in support of the '793 patent IPR, stating that “[i]nhaled treprostinil is also approved to treat a broader range of pulmonary hypertension patients than the therapeutics available at the time of the invention.” (DTX0101, Waxman IPR Decl. at LIQ\_PH-ILD\_00102081 ¶¶ 95-96.) Dr. Waxman opined that “[a]t the time of the claimed invention and even as of today, there are no other therapies approved for the treatment of pulmonary hypertension in patients with interstitial lung disease.” (*Id.* at LIQ\_PH-ILD\_00102081 ¶ 96.) Furthermore, UTC submitted a letter to the FDA on February 12, 2024, acknowledging that the '793 patent claims also cover the approved PH-ILD indication. (*See* DTX0028, Feb. 12, 2024, FDA Letter at LIQ\_PH-ILD\_00000852.) Therefore, even if any unmet need existed with respect to the treatment of PH-ILD, UTC admitted that the invention in the '793 patent satisfied that need. (Anticipated Testimony of Dr. Channick.)

746. Physicians were already treating PH-ILD patients with inhaled treprostinil. (Anticipated Testimony of Dr. Channick.) Indeed, the INCREASE study used the exact same drug, Tyvaso, with the exact same dosing as disclosed in Faria-Urbina 2018 and Agarwal 2015,

and merely tested it in a larger population than what Faria-Urbina 2018 and Agarwal 2015 disclosed. Therefore, it further confirmed that Tyvaso® as used in real world practice satisfied the treatment needs of PH-ILD patients. (Anticipated Testimony of Dr. Channick.)

747. Dr. Nathan has argued that the '793 patent fails to disclose many of the claimed elements of the claimed invention of the '327 patent and, therefore, could not have satisfied the long-felt and unmet need for a PH-ILD therapeutic that improves exercise capacity for PH-ILD patients. (Anticipated Testimony of Dr. Nathan.) However, these purported differences between the two patents do not avoid the fact that UTC previously argued: (a) the '793 patent covers the approved PH-ILD indication, including improving exercise capacity (DTX0002), and (b) the '793 patent satisfies a long-felt unmet need including treatment of PH-ILD. Dr. Nathan has further asserted that there could be a need for hemodynamic improvement satisfied by the '793 patent that nevertheless failed to fulfill the additional significant long-felt but unmet need to improve exercise capacity in patients with PH-ILD. (Anticipated Testimony of Dr. Nathan.) However, when arguing for long-felt unmet need in the '793 IPR, UTC did not make any such distinction between hemodynamic effects and improvements to exercise or other endpoints. (DTX0110.) Further, UTC specifically told the FDA that the '793 patent is directed to the PH-ILD indication in the Tyvaso label, not some hemodynamic effect. (DTX0028, Feb. 12, 2024 FDA Letter (LIQ\_PH-ILD\_00000847) at LIQ\_PH-ILD\_00000852.) UTC's position also ignores the fact that treprostinil is a vasodilator with an accepted mechanism of action that treats by improving hemodynamics. (Anticipated Testimony of Dr. Channick.)

**i. The Prior Art Does Not Teach Away from the Claimed Invention**

748. Dr. Nathan has argued that the prior art teaches away from the claimed invention, relying on the same evidence he identified regarding failed studies. (Anticipated Testimony of Dr.



Nathan.) However, all of the previous failed studies involved a different drug class and/or different route of administration, or were used to treat different disease states. (Anticipated Testimony of Dr. Channick.) Dr. Nathan is incorrect to assert that the previous studies signaled that using treprostinil to treat PH-ILD was unlikely to yield a successful outcome. (Anticipated Testimony of Dr. Channick.) Prior to 2020, UTC's CEO publicly stated that physicians had seen "unmistakable signals" of treprostinil's effectiveness in PH-ILD patients, physicians across the country regularly prescribed Tyvaso® off-label to PH-ILD patients, and concluding "This drug works." (DTX0003, UTC 2018 Earnings Call Transcript ((LIQ\_PH-ILD\_00000001) at LIQ\_PH-ILD\_00000010.) Moreover, the claimed invention was far from a departure from the prior art, including the '793 patent, Faria-Urbina 2018, Saggar 2014, and Agarwal 2015; rather, the invention is nothing more than the results of the confirmatory INCREASE study. (Anticipated Testimony of Dr. Channick.) Even if Saggar 2014, Agarwal 2015, and Faria-Urbina 2018 were merely "hypothesis generating," that cannot support teaching away because UTC itself obtained patent claims in the '327 patent based on FVC data that Dr. Nathan admitted were hypothesis generating. (Anticipated Testimony of Dr. Channick.)

### **3. No Copying of Others**

749. UTC may argue that Liquidia copied the claimed subject matter of the '327 patent. However, there is no dispute that YUTREPIA was developed before the claims of the '327 patent issued and that Liquidia included the PH-ILD indication before the November 28, 2023 issue date of the '327 patent. UTC first sued Liquidia with respect to PH-ILD on September 5, 2023. (D.I. 1, Compl. (Sept. 5, 2023).) Liquidia thus could not have copied a patent claim that did not exist when YUTREPIA was developed and submitted for PH-ILD. Moreover, YUTREPIA simply discloses the same indication as disclosed in the prior art Faria-Urbina 2018 and Agarwal 2018

references using the same drug (treprostinil) with the same route of administration. (Anticipated Testimony of Dr. Channick.)

750. Nonetheless, the '327 patent claim 1 copied Faria-Urbina 2018 and Agarwal 2015. Dr. Waxman testified that the patient population in INCREASE, which is the '327 patent, was the same as Faria-Urbina 2018 and that the INCREASE study obtained its results using the same dosing as Faria-Urbina 2018. (Waxman Depo. Tr. at 224:22-25.) Thus, the inventors of the '327 patent simply copied what was already known. (Anticipated Testimony of Dr. Channick.)

751. UTC may also argue that Liquidia's reliance on the INCREASE study results to support the PH-ILD indication for YUTREPIA is evidence of copying. (Anticipated Testimony of Dr. Nathan.) However, Liquidia's use of the 505(b)(2) approval pathway has no bearing on whether Liquidia "copied" patent claims and in approving Yutrepia the FDA relied on additional clinical studies performed by Liquidia. Nor does inclusion of certain information from the Tyvaso label evidence any copying of patent claims. Furthermore, the INCREASE study does not align precisely with the Asserted Claims because the Asserted Claims do not incorporate the specific inclusion and exclusion criteria used in the INCREASE study. (Anticipated Testimony of Dr. Channick.)

#### **4. No Failure of Others**

752. UTC has maintained that numerous "negative" studies show the failure of PAH drugs to improve exercise capacity in PH-ILD patients. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan testified that "the history of medicine is such that if you have one negative study, you don't necessarily give up" and there are many "negative studies in medicine that have subsequently been followed by positive studies." (Nathan Depo. Tr. at 42:7-24.)

753. Dr. Nathan previously identified a number of clinical studies that he suggests would discourage a POSA from using a Group 1 PAH therapy like inhaled treprostinil in a patient with

PH-ILD. (DTX0625, Nathan PI Decl., ¶¶ 78-87, 167, 183, 184, 190-199, 207-209.) These studies were conducted on drugs of different classes and/or were administered by different routes or in different diseases (ILD vs. COPD), including the BPHIT Study (examining bosentan) and the RISE-IIP study (examining rigociguat), as well as the STEP-IPF, INSTAGE, and Sildenafil with Pirfenidone studies (examining oral sildenafil alone or in combination with other drugs). Their teachings are thus not directly informative of what a POSA would expect using inhaled treprostinil in a PH-ILD patient.

754. In fact, Dr. Waxman testified, with respect to the RISE-IIP study in particular, that the stoppage of this study in no way discouraged his continued use of Tyvaso® to treat PH-ILD patients because: “[i]t’s a different class of drug, different administration, different type of side-effects.” (Waxman Depo. Tr. at 111:8-111:8-112:6.) Dr. Tapson, another INCREASE study steering committee member also stated that at no time from 2009 up to starting the INCREASE study did he ever consider stopping his use of Tyvaso® to treat PH-ILD patients. (See Tapson Depo. Tr. at 44:22-45:14; 53:24-55:1.) Even Dr. Nathan admitted that for “a different drug or a different drug formulation given by a different system, the results can be entirely different than what has been seen or what might be seen with another drug.” (Nathan Depo. Tr. at 226:7-15.)

755. In 2017, Dr. Waxman spoke publicly at the 12<sup>th</sup> Annual John Vane Memorial Symposium where he discussed these negative or mixed-result studies and stated that they were likely inconclusive because of poor study design. (See DTX0138, LIQ\_PH-ILD\_00147322 at 6:40–7:30; DTX0140, 2017 Waxman Tr. at 7:3-8:8.) Dr. Waxman expounded on this point in his testimony, stating that the “studies were small, they were poorly conducted, poorly designed, [and] often didn’t include right heart cath.” (Waxman Depo. Tr. at 80:11-22.) Dr. Rajan Saggarr noted that when designing a study for the use of Remodulin in PH-ILD patients, the design team “were

also guided by the fact that many PH-ILD studies had failed with other PH therapies . . . due to trial design.” (Rajan Sagar Sept. 17, 2024 Depo. Tr. at 126:15-22.) He further testified that he believed these studies with drugs such as bosentan and riociguat were not focused on the “degree of pulmonary hypertension being studied” and that a better study design would focus on ILD patients with moderate to severe pulmonary hypertension. (*Id.* at 126:25-25.) And Dr. Smith confirmed that he was not aware of a single study evaluating inhaled treprostinil in PH-ILD patients that was negative or inconclusive. (Smith Depo. Tr. at 129:1-6.) Thus, these alleged “failures” of different drugs do not constitute failure of others. (Anticipated Testimony of Dr. Channick.)

756. If one were to credit the great skepticism and pessimism on which UTC and Dr. Nathan have opined, it is unlikely that researchers would have planned and implemented the presumably multi-million-dollar clinical study INCREASE at all. To the contrary, UTC was so optimistic that inhaled treprostinil worked in PH-ILD patients that its CEO, Martine Rothblatt, relayed to investors in 2018 (two years before the INCREASE study results were obtained and the ’327 patent filed) that physicians in the field had seen “unmistakable signals” of treprostinil’s effectiveness and that doctors had told UTC that “this drug works even better in [Group 3 patients including PH-ILD] than in the Group [1] indication in terms of, at least, the exercise ability[.]” (DTX0003, UTC 2018 Earnings Call Transcript at LIQ\_PH-ILD\_00000010.) As Dr. Rothblatt said “This drug works.” (*Id.*)

## **5. No Proof of Skepticism of Others**

757. UTC may argue that others were skeptical. However, multiple practicing physicians have consistently testified that they used Tyvaso since 2009, without interruption, to treat PH-ILD patients. Further, when asked if Dr. Waxman was aware of anyone expressing doubt as to whether Tyvaso® is effective in PH-ILD, he said that only “narrow-minded conservative

physicians” who believed “that if you deviate from the guidelines, you aren’t doing the right thing” had any doubt. (Waxman Depo. Tr. at 226:11-17.)

758. Even Dr. Rothblatt publicly stated optimism, as opposed to skepticism, that inhaled treprostinil works to improve the exercise capacity in PH-ILD patients. Notably, her statements were based on speaking with doctors, including Dr. Waxman, and reviewing posters and presentations on the topic. (DTX0003, UTC 2018 Earnings Call Transcript at LIQ\_PH-ILD-00000010.)

759. Indeed, Dr. Nathan previously testified in this case that UTC never expressed any “skepticism” that the INCREASE study would not be successful. (Anticipated testimony of Dr. Nathan.)

## **6. No Commercial Success**

760. UTC has argued that Tyvaso®’s commercial success is attributed to the claimed treatment of PH-ILD patients. (Anticipated Testimony of Dr. Selck.) However, UTC cannot demonstrate that Tyvaso’s sales for the treatment of PH-ILD are due to the merits of the ’327 patent’s claimed invention beyond what was readily available in the prior art. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Mr. Kidder.) Treating PH-ILD with inhaled treprostinil was well known in the art long before April 17, 2020, and the ’327 patent merely studied inhaled treprostinil in a larger patient population. (Anticipated Testimony of Dr. Channick.) Moreover, the approved indication for Tyvaso® and Tyvaso DPI® in PH-ILD is: “Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (DTX0360, 2021 Tyvaso® Label at UTC\_PH-ILD\_010744; DTX0358, 2022 Tyvaso DPI® Label (UTC\_PH-ILD\_010709).) The approved indication says nothing with respect to NT-proBNP, FVC, clinical exacerbations, time to clinical worsening, or specific improvements in the 6MWD test. Thus, UTC cannot establish a nexus between any alleged

success of Tyvaso® or Tyvaso DPI® and the dependent claims of the '327 patent. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Mr. Kidder.)

761. UTC cannot show that Tyvaso's commercial success is due to the inventions claimed in the '327 patent, because UTC has blocked all competition for treprostinil products for the treatment of PH-ILD and Tyvaso® and Tyvaso DPI® simply include the same drug, dosing and PH-ILD indication disclosed in the prior art. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Mr. Kidder.) YUTREPIA is not yet commercially available and there are no other FDA approved treprostinil products for PH-ILD. Thus, the success of Tyvaso® and Tyvaso DPI® is due to the lack of any competition. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Mr. Kidder.)

762. Initially, UTC obtained orphan drug exclusivity for Tyvaso® that prevented additional inhaled treprostinil products from being approved by the FDA and commercialized. UTC continues to seek ways to delay the entry of additional inhaled treprostinil products. On February 20, 2024, UTC filed a Complaint against the FDA to force Liquidia to make additional submissions to the FDA and thereby delay approval of Liquidia's application. (DTX0614, *United Therapeutics Corp. v. FDA*, No. 1:24-cv-0484-JDB, Dkt. 1 (D.D.C. Feb. 20, 2024).) Additionally, several companies have sought to make generic treprostinil products, but in each instance, UTC has settled litigation that prevented those companies from marketing their products. (See *United Therapeutics Corp. v. Watson Lab'ys, Inc.*, No. 3:15-cv-05723 (D.N.J. 2015); *United Therapeutics Corp. v. Par Sterile Products, LLC*, No. 3:16-cv-08548 (D.N.J. 2016); *United Therapeutics Corp. v. Par Sterile Products, LLC*, No. 1:16-cv-01066 (D. Del. 2016); *United Therapeutics Corp. v. Actavis Lab'ys FL, Inc.*, No. 3:16-cv-03642 (D.N.J. 2016); *United Therapeutics Corp. v. Actavis Lab'ys FL, Inc.*, No. 3:16-cv-01816 (D.N.J. 2016); *United Therapeutics Corp. v. Teva Pharms.*

*USA, Inc.*, No. 3:14-cv-05498 (D.N.J. 2014); *United Therapeutics Corp. v. Sandoz, Inc.*, No. 3:14-cv-05499 (D.N.J. 2014); *United Therapeutics Corp. v. Sandoz, Inc.*, No. 3:13-cv-00316 (D.N.J. 2013); *United Therapeutics Corp. v. Sandoz, Inc.*, No. 3:12-cv-01617 (D.N.J. 2012).) Further, UTC has systematically used its patents covering treprostinil, and continues to attempt to obtain new patents, including the '793 patent and '327 patent, to block others from developing and commercializing treprostinil products. (*See Acorda Therapeutics, Inc. v. Roxane Lab 'ys, Inc.*, 903 F.3d 1310, 1338-39 (Fed. Cir. 2018).)

763. The '793 patent, which issued years before the '327 patent, claims the use of inhaled treprostinil as a therapy for PH-ILD patients. Thus, the nexus between the invention of the '327 patent and any purported commercial success has to be a nexus between the additional scope (if any) of the '327 claims over the pre-existing '793 claims. (Anticipated Testimony of Mr. Kidder.) Dr. Selck has provided analysis related to the effect of FDA approval for the PH-ILD indication – an invention claimed in the '793 Patent – and sales of Tyvaso. (Anticipated Testimony of Mr. Kidder.) Thus, Dr. Selck and UTC have failed to show that a nexus exists between commercial success and the claimed invention over the prior art.

764. Dr. Selck has argued that the increase in sales after the FDA approval of Tyvaso for PH-ILD is the result of the FDA approval. (Anticipated Testimony of Dr. Selck.) However, a more sophisticated analysis shows that FDA approval for the PH-ILD indication did not have a statistically significant effect on the sales of Tyvaso when UTC's marketing efforts and the approval of Tyvaso DPI® are considered. (Anticipated Testimony of Mr. Kidder.)

765. Tyvaso was approved for PAH in 2009. In 2010, the FDA granted orphan drug designation for Tyvaso, which resulted in an orphan exclusivity period that expired in July 2016. (DTX0239, UTHR, Form 10-K, FYE Dec. 31, 2023 at LIQ\_PH-ILD\_00151348.) Between 2017

and 2019, UTC enrolled patients in a phase III registration study called INCREASE designed to evaluate the safety and efficacy of Tyvaso “in patients with WHO Group 3 pulmonary hypertension associated with interstitial lung disease (specifically associated with idiopathic pulmonary fibrosis or combined pulmonary fibrosis and emphysema),” also referred to as PH-ILD. (DTX0243, UTHR, Form 10-K, FYE Dec. 31, 2019, p. 14.) The INCREASE study was first publicly disclosed in 2015.

766. The FDA granted approval for nebulized Tyvaso for PH-ILD in April 2021. (DTX0664, United Press Release, United Therapeutics Announces FDA Approval and Launch of Tyvaso for the Treatment of Pulmonary Hypertension Associated with Interstitial Lung Disease, 2021-04-01, accessed 2024-03-27 at <https://www.prnewswire.com/news-releases/united-therapeutics-announces-fda-approval-and-launch-of-tyvaso-forthe-treatment-of-pulmonary-hypertension-associated-with-interstitial-lung-disease-301260212.html>.) Along with approval, nebulized Tyvaso for PH-ILD received three years of regulatory exclusivity through March 31, 2024. (UTC’s First Amended Complaint, November 30, 2023, ¶ 12.) The FDA approved Tyvaso DPI for PAH and PH-ILD in May 2022, and granted regulatory exclusivity through May 23, 2025. (DTX0239, UTHR, Form 10-K, FYE Dec. 31, 2023 at LIQ\_PH-ILD\_00151338.)

767. Manufacturers of brand-name drugs like Tyvaso are protected from generic competition through two forms of government-granted exclusivity. The first is regulatory exclusivity, granted at the time of FDA approval, which sets a minimum period before generic alternatives can be introduced. (DTX0194, Kesselheim, A., et al., *Determinants of Market Exclusivity for Prescription Drugs in the United States*, JAMA Intern. Med. 177(11):1658-64, Abstract, accessed 2025-02-18 at <https://pubmed.ncbi.nlm.nih.gov/28892528/>.) The second form



is patent protection, which generally provides a defined period during which only patented or licensed versions can be marketed.

768. Treprostinil is in a class of compounds called prostacyclin analogues. For PAH, prostacyclin analogues as a class were used a minority of the time for patients receiving injections. (DTX0189, Hendriks, P.M., et al., *The evolution of survival of pulmonary arterial hypertension over 15 years*, Pulm Circ., 12(4):e12137 at LIQ\_PH-ILD\_00148992.) UTC offers four different treprostinil therapies: Remodulin (injected), Orenitram (oral), Tyvaso (inhaled, nebulized) and Tyvaso DPI (inhaled, powder).

769. Dr. Selck has argued that the '793 patent was not a blocking patent in the sense that it did not hinder third parties from developing and commercializing a product with the innovation claimed in the '327 patent. (Anticipated Testimony of Dr. Selck.) In essence, Dr. Selck is arguing that the incentive to develop and commercialize the claimed invention of the '327 was stronger than the disincentive posed by the rights conferred by the '793 patent. (Anticipated Testimony of Mr. Kidder.) However, the '793 patent also claimed the use of inhaled treprostinil to treat PH-ILD.

770. Dr. Selck has not considered the claims of the '793 patent as they relate to a nexus. (Anticipated Testimony of Mr. Kidder.) Nor does he consider the fact that UTC sued Liquidia for patent infringement on the '793 patent in September 2023, based solely on Liquidia's inclusion of the PH-ILD indication. (*United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 1:23-cv-975 (RGA), D.I. 1 (D. Del., Sept. 5, 2023).)

771. Dr. Selck has not and cannot point to any evidence that the '327 patent played any role in obtaining FDA approval for the PH-ILD indication. (Anticipated Testimony of Mr. Kidder.) Dr. Selck has failed to consider that Tyvaso's commercial success – both before and after

FDA approval for PH-ILD – is largely attributable to factors other than the invention claimed in the '327 patent. For example, UTC benefited from a three-year regulatory exclusivity period following FDA approval for PH-ILD, which includes the specific period Dr. Selck considered – Q2 2021 through Q1 2022 – meaning that no generic or competing inhaled treprostinil products could enter the market. (Anticipated Testimony of Mr. Kidder.) Other issued UTC patents covering treprostinil, separate from the '327 patent, may have also discouraged competition during that period. In the absence of alternatives, sales during this period reflect market conditions where physicians seeking to prescribe an FDA-approved inhaled treprostinil for PH-ILD or PAH had no choice but to use Tyvaso. (Anticipated Testimony of Mr. Kidder.)

772. Factors that affected Tyvaso's sales that Dr. Selck has not considered include:

- a. Prior use of inhaled treprostinil for treating PH-ILD as described by Drs. Channick and Hill;
- b. Regulatory exclusivity, which precludes competition and prevents any evaluation of sales by competitors during the exclusivity periods;
- c. Evidence of the safety and efficacy of Tyvaso for PH-ILD, which is required for FDA approval, and which increases physician awareness and confidence;
- d. Indication labeling, which also increases physician awareness, confidence, and likelihood of prescribing;
- e. Prior patent exclusivity for the PH-ILD indication with respect to the '793 patent, which also precluded competition and sales by competitors during the exclusivity period;

- f. UTC's sales and marketing efforts to promote Tyvaso and Tyvaso DPI for PH-ILD; and,
- g. UTC's proprietary delivery devices.

773. [REDACTED]

[REDACTED] (Anticipated Testimony of Dr. Selck.) [REDACTED]

[REDACTED] (Anticipated Testimony of Dr. Selck.) However, this analysis assumes that any increase in sales after FDA approval of the PH-ILD indication for Tyvaso is a result of the FDA approval without looking at other factors that might have contributed to Tyvaso sales. (Anticipated Testimony of Mr. Kidder.) Importantly, even if the increase in sales can be attributed, in some capacity to FDA approval, that is not the nexus to the claimed invention required for commercial success. (Anticipated Testimony of Mr. Kidder.) For example, FDA approval allowed UTC to begin marketing Tyvaso as a treatment for PH-ILD which had to increase the number and share of PH-ILD commercial patients separate and apart from the claimed invention of the '327 Patent. (Anticipated Testimony of Mr. Kidder.) Since doctors were prescribing Tyvaso for patients with PH-ILD prior to FDA approval for the PH-ILD indication, it is also unclear what portion of any increase in the number of prescriptions for the PH-ILD indication is from patients who would not have otherwise been prescribed Tyvaso. (Anticipated Testimony of Mr. Kidder.)

774. The lack of competition due to regulatory exclusivity makes the observed sales volume inevitable rather than indicative of commercial success attributable to the '327 patent. (Anticipated Testimony of Mr. Kidder.) Any product with exclusivity in a critical therapeutic area would likely generate sales, regardless of patented technology. (Anticipated Testimony of Mr.

Kidder.) Moreover, Dr. Selck’s quantitative analyses have failed to consider or account for sales and profit increases caused by UTC’s considerable investments in sales & marketing, including efforts to increase education and awareness of PH-ILD screening among physicians. (Anticipated Testimony of Mr. Kidder.) Once it obtained FDA approval, UTC could lawfully promote the use of Tyvaso for PH-ILD. (Anticipated Testimony of Mr. Kidder.) Dr. Selck’s analysis also ignores any effect of the benefits associated with UTC’s proprietary TD-300 nebulizer. (Anticipated Testimony of Mr. Kidder.) Thus, Dr. Selck’s characterization of sales as “significant” lacks analytical rigor and suffers from confounding or hidden variables. (Anticipated Testimony of Mr. Kidder.)

775. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] || [REDACTED]

[REDACTED] || [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



776. [REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

777. [REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

778. It [REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]

779. When examining the effect of an event on a particular dependent variable, most economists would use a regression to discern whether the particular event had a statistically significant effect on the dependent variable. (Anticipated Testimony of Mr. Kidder.) In this case,

the dependent variable is sales of Tyvaso and the event is the FDA approval of nebulized Tyvaso for PH-ILD. (Anticipated Testimony of Mr. Kidder.)

780. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

781. Drug pricing and reimbursement policies play an important role in determining market performance, often independent of the patented invention itself. Government reimbursement decisions, private insurer coverage, and pricing strategies influenced by competitive and regulatory dynamics can significantly impact sales volume and revenue. These factors can create demand and shape access irrespective of the patent's technical contribution. (Anticipated Testimony of Mr. Kidder.)

782. FDA approval is neither contingent upon nor supported by the existence of a patent application or issued patent and the success of a clinical trial depends on multiple factors beyond the claimed method in the '327 Patent, including trial design, patient selection and retention, endpoint relevance, regulatory compliance, and the drug's safety and efficacy profile. Additionally, factors like the specific indication, an assessment of the "acceptable risk," statistical power of clinical results, and market dynamics play a critical role in determining whether a treatment gains regulatory approval and widespread adoption. UTC's press releases and public

statements are evidence of money and efforts by UTC to promote Tyvaso. In particular, the INCREASE study results were marketed by UTC and used by UTC to encourage more doctors to screen ILD patients for PH. Thus, to the extent that these publications increased awareness of and, subsequently, prescriptions for Tyvaso for patients with PH-ILD, they represent an independent driver of Tyvaso's commercial success. (Anticipated Testimony of Mr. Kidder.)

783. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

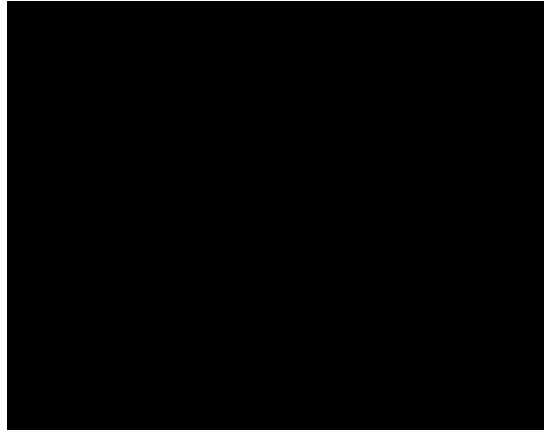
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784. [REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

785. Tyvaso is administered to PAH and PH-ILD patients using proprietary delivery devices that offer benefits independent of the patented method. These proprietary benefits have contributed to Tyvaso's commercial success. (Anticipated Testimony of Mr. Kidder.) The claims of the '327 Patent do not relate to the particular inhalation device technology used with Tyvaso for PH-ILD. Thus, any benefits patients receive from the device that promote initial or continued use of Tyvaso for PH-ILD would drive commercial success based on non-patented elements, that are independent of the claims in the '327 Objective Indicia of Obviousness



## 7. Objective Indicia of Obviousness

786. As noted in Section V.B., multiple physicians, working independently, in different facilities, in different parts of the country, began prescribing inhaled treprostinil to treat PH-ILD patients shortly after Tyvaso was approved to treat PAH in 2009. All of these physicians observed improvements in their patients, including in their exercise capacity. The simultaneous use of Tyvaso, by physicians making independent decisions for the treatment of PH-ILD, is evidence that the claimed method of treatment is merely the product of the ordinary skill of a POSA at the time. (Anticipated Testimony of Dr. Channick; Anticipated Testimony of Dr. Hill.)

787. For example, Dr. Channick and his colleagues at UCSD in San Diego prescribed Tyvaso to treat PH-ILD patients almost immediately after it was approved to treat PAH in 2009. (Anticipated Testimony of Dr. Channick.) Meanwhile, Dr. Hill, who was based in Massachusetts at the time, began prescribing Tyvaso to PH-ILD patients within one year of its approval to treat PAH. (Anticipated Testimony of Dr. Hill.)

788. Additionally, Dr. Tapson testified that he began treating PH-ILD patients with Tyvaso as early as 2009. (Tapson Depo. Tr. at 160:20-164:18; *see also id.* at 40:8-21, 41:22-43:14, 46:2-48:4, 52:13-23.) Dr. Tapson was a practicing physician at Duke University Medical Center, in North Carolina at the time and then later moved to Cedars in California. (Tapson Depo. Tr. at 43:16-44:21 (discussing Tyvaso use for PH-ILD patients at Duke).)

789. Dr. Waxman also used Tyvaso off-label to treat PH-ILD patients as soon as it was commercially available. (Waxman Depo. Tr. at 49:22-50:5.) Dr. Waxman was a practicing physician in Boston when Tyvaso was approved for PAH in 2009. (*See* DTX0297, Waxman Depo. Ex. 1 (Waxman CV).)

790. Drs. Rajan Saggar, Rajeev Saggar, and Kishan Parikh further confirmed that they and their colleagues prescribed inhaled treprostinil off-label to treat patients with PH-ILD as early as 2009. Specifically, Dr. Rajan Saggar testified that, from the time Tyvaso was approved in 2009 up until 2020, his group at UCLA treated “somewhere between 75 and a 100” PH-ILD patients with Tyvaso. (Rajan Saggar Sept. 2024 Depo. Tr. at 143:12-23.) Dr. Rajeev Saggar confirmed that he used Tyvaso off-label for the treatment of PH-ILD patients around 2010 and that he prescribed the dose described in the Tyvaso label for PAH. (Rajeev Saggar Depo. Tr. at 222:13-223:19 (objections omitted); *see also id.* at 202:8-203:1.)

791. Thus, numerous physicians were prescribing Tyvaso, to treat PH-ILD, shortly after its approval in 2009. In doing so, physicians were prescribing Tyvaso using the dose described in the Tyvaso label for PAH. (Rajeev Saggar Depo. Tr. at 222:13-223:19 (objections omitted); *see also id.* at 202:8-203:1.)

#### **X. WRITTEN DESCRIPTION**

792. Claim 9 depends from claim 1 and further requires that administration of treprostinil result in “statistically significant improve[ment] of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks[.]” (’327 patent at Claim 9.) Claim 10 depends from claim 9 and, thus, also requires a statistically significant improvement in FVC. (’327 patent at Claim 10.) In addition, Claim 10 requires an improvement in FVC by “at least 20 ml after 8 weeks, 12 weeks, or 16 weeks” after administration. (*Id.*)

793. The ’327 patent defines FVC as “the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible, as measured by spirometry.” (*Id.* at 13:4-

7.) The results of an FVC test using spirometry are expressed in mL. (Anticipated Testimony of Dr. Channick; '327 patent at Tables 1 and 2.)

794. Because claim 10 depends from claim 9, and requires an FVC result expressed in mL, the meaning of FVC in claim 9 includes absolute FVC. (Anticipated Testimony of Dr. Channick.)

795. The '327 patent also makes reference to percent predicted FVC. ('327 Patent at Tables 1 and 2) Percent predicted FVC is different from absolute FVC, as percent predicted FVC normalizes the FVC value based on characteristics of height, age, sex, etc. (Tapson Depo. Tr. at 139:1-18; Deng Depo. Tr. at 105:22-107:7; Waxman Depo. Tr. at 106:8-107:9; Rajan Saggur Sept. 17, 2024 Depo. Tr. at 47:22-49:14.) Because the '327 patent includes both absolute and percent predicted FVC, FVC in claim 9 includes both absolute and percent predicted FVC. (Anticipated Testimony of Dr. Channick.)

796. Given that claims 9 and 10 depend on claim 1, a POSA would understand that these claims cover statistically significant improvements in absolute *and* percent predicted FVC in the entire PH-ILD population claimed (including, but not limited to, the IPF, IIP, CPFE, and CTD subpopulations). (Anticipated Testimony of Dr. Channick.)

797. There is no data in Tables 1, 2, and 3 demonstrating that the entire PH-ILD population experienced statistically significant improvements in absolute FVC following administration of inhaled treprostinil. ('327 patent at Tables 1-3; Anticipated Testimony of Dr. Channick.) Tables 1, 2, and 3 of the '327 patent provide data on FVC measurements. (*Id.*) Table 1 shows all the patients treated in the INCREASE study (i.e., the intent-to-treat (ITT) population), which was 142 patients who received inhaled treprostinil. ('327 patent at Table 1.) The p-values reported in Table 1 at weeks 8 and 16 for FVC are 0.3453 and 0.2106, respectively. (*Id.*) To be

considered statistically significant, a p-value has to be at or below 0.05. (Anticipated Testimony of Dr. Channick.) As confirmed by co-inventor, Dr. Deng, none of the ITT population in Table 1 achieved a statistically significant reduction in FVC as required by claims 9 and 10. (Deng Depo at 108:19-109:1.) Because the claims include absolute FVC, Table 1 does not provide adequate written description support for the full scope of claims 9 and 10. (Anticipated Testimony of Dr. Channick.)

798. Tables 2 and 3 show data from two different PH-ILD subpopulations—IIP and IPF, respectively. ('327 patent at Tables 2, 3.) In Table 2, the absolute FVC value for the PH-ILD Etiology: IIP at week 8 was 0.2467 (58 patients), which is not a statistically significant improvement in FVC, while the absolute FVC for the PH-ILD Etiology: IIP at week 16 was statistically significant (p-value of 0.0229) (52 patients). (*Id.*) Table 2 provides statistically significant results for percent predicted FVC at weeks 8 and 16 in the IIP subgroup (58 and 52 patients, respectively). (*Id.*)

799. Table 3 provides FVC values for the PH-ILD IPF subgroup. (*Id.* at Table 3.) In Table 3, the absolute FVC value for the PH-ILD with IPF subgroup at week 8 was 0.1128 (31 patients), which is not a statistically significant improvement in FVC, while the FVC for the PH-ILD with IPF subgroup at week 16 was statistically significant (p-value of 0.0108) (28 patients). (*Id.*; Deng Depo. Tr. at 119:5-11.) Table 3 provides statistically significant results for percent predicted FVC at weeks 8 and 16 in the IPF subgroup. (*Id.*)

800. Because the data in Tables 2 and 3 only show a subset of PH-ILD patients (IIP and IPF), they do not represent the full scope of the PH-ILD population in claims 9 and 10. (Anticipated Testimony of Dr. Channick.) Although Tables 2 and 3 provide statistically significant results for absolute FVC at week 16, and percent predicted FVC at weeks 8 and 16 for the IIP and

IPF subgroups, Tables 2 and 3 do not represent the entire PH-ILD population as claimed in claims 9 and 10, and thus they also do not convey to a POSA that the inventors were in possession of the full scope of claims 9 and 10. (Anticipated Testimony of Dr. Channick.)

801. Table 10 also provides FVC values associated with the clinical trial described in Example 3, which is the INCREASE study. ('327 Patent at Table 10.) Table 10, like Table 1 demonstrates that absolute FVC taken at weeks 8 and 16 for the entire PH-ILD patient population did not provide a statistically significant improvement (p-values of 0.35 and 0.21, respectively). (Anticipated Testimony of Dr. Channick.) A statistically significant improvement was seen with percent predicted FVC at weeks 8 and 16 (p-values of 0.01 and 0.03, respectively). Table 10, like Table 1, does not establish the inventors were in possession of a statistically significant improvement in FVC for the entire PH-ILD population encompassed by claims 9 and 10. (Anticipated Testimony of Dr. Channick.) Accordingly, Table 10 also does not provide written description support for claims 9 and 10. (Anticipated Testimony of Dr. Channick.)

802. Absolute FVC values in Tables 1 and 10 were not statistically significant in the entire PH-ILD population. (Anticipated Testimony of Dr. Channick.) While percent predicted FVC values in Tables 1 and 10 were statistically significant at weeks 8 and 16, this represents only half of the FVC values encompassed by claims 9 and 10. (Anticipated Testimony of Dr. Channick.) Because FVC means both absolute and percent predicted FVC, the data in the '327 patent demonstrates that PH-ILD patients did not experience a statistically significant improvement in one of the two identified FVC values, thus there is no written description support for the full scope of claims 9 and 10. (Anticipated Testimony of Dr. Channick.)

803. Tables 2 and 3, moreover, would not cure the deficiencies in Tables 1 and 10 because they are limited to PH-ILD subgroups (IIP and IPF), and claims 9 and 10 are directed to

the entire PH-ILD patient population disclosed in the specification. (Anticipated Testimony of Dr. Channick.) Thus, Tables 2 and 3 do not convey that the inventors were in possession of statistically significant improvements in FVC for the entire PH-ILD population claimed in claims 9 and 10 and thus Table 2 and 3 do not provide sufficient written description support of the claims. (Anticipated Testimony of Dr. Channick.)

804. With respect to claim 9, Dr. Wertheim and UTC have taken the position that a POSA would understand that the inventors were in possession of a method of performing independent claim 1 of the '327 patent in which the administration of inhaled treprostinil produced statistically significant improvement of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering, because Examples 1 and 3 of the '327 specification disclose that the patients administered inhaled treprostinil as part of the INCREASE study exhibited a statistically significant increase in their percent predicted FVC. (Anticipated Testimony of Dr. Wertheim.) Written description support for claim 1 of the '327 patent does not mean the '327 patent also provides written description support for claim 9. Moreover, the statistically significant increase in percent predicted FVC as exhibited in the INCREASE study, was achieved in the entire study population (ITT) as well as in the IIP and IPF subgroup at all measured timepoints. (Anticipated Testimony of Dr. Channick.) Claim 9 requires a statistically significant result in both percent predicted and absolute FVC as well as such a result in the entire PH-ILD population encompassed by claim 9. (Anticipated Testimony of Dr. Channick.) Because the '327 patent fails to demonstrate a statistically significant FVC result for the full scope of claim 9, the results in INCREASE, as noted above, do not satisfy the written description requirement for claim 9. (Anticipated Testimony of Dr. Channick.)

805. Dr. Wertheim and UTC are of the opinion that a POSA would preferentially focus on percent predicted FVC in favor of absolute FVC because the POSA would understand percent predicted FVC to be a more valuable endpoint. (Anticipated Testimony of Dr. Wertheim.) The '327 patent does not describe a preference for percent predicted FVC over absolute FVC. The fact that claim 10 is directed to absolute FVC proves the '327 patent does not favor percent predicted over absolute FVC. Further, column 22:55-65 of the '327 patent provides baseline FVC in absolute values: ITT 28.7 mL and 44.40 mL in FVC at Weeks 8 and 16; IIP 46.48 mL and 108.18 mL ( $p=0.0229$ ) at Weeks 8 and 16; IPF 84.52 mL and 168.52 mL ( $p=0.0108$ ) at Weeks 8 and 16. ('327 patent at 22:55-65.) Example 2 points to measurements in both absolute and percent predicted FVC. ('327 patent at 25:52-55.)

806. Claim 10 depends from claim 9 and additionally requires that the administration of treprostinil to the PH-ILD patient improve the patient's FVC "by at least 20 mL after 8 weeks, 12 weeks, or 16 weeks of the administering." ('327 patent at Claim 10.) Thus, since a POSA would not understand the inventors to be in possession of the invention disclosed in claim 9, a POSA would also not understand the inventors to be in possession of the invention disclosed in claim 10.

807. Dr. Wertheim, referring to the INCREASE study results in Examples 1 and 3, takes the position that although several of the datapoints were not shown to be statistically significant, they all exhibit a positive trend and a POSA would not read claim 10 of the '327 patent to require that the 20 mL increase in absolute FVC volume be statistically significant. (Anticipated Testimony of Dr. Wertheim.) However, claim 10 depends from claim 9, meaning that a POSA would understand that claim 10 requires that the improvement in FVC be statistically significant as required by claim 9. (Anticipated Testimony of Dr. Channick.) Thus, the specification does not provide written description support for claim 10.

808. The statistically significant increase in FVC reported in the '327 patent is based on the difference between placebo and treatment arms. Specifically, the p-value reported in Tables 1-3 and Table 10 is associated with an "Estimated Difference" between the placebo and treatment groups at week 8 and week 16. ('327 patent at Table 1, Table 2, Table 3, Table 10.) Therefore, the analysis provided in the patent specification shows a statistically significant difference in absolute and percent predicted FVC between treatment and placebo groups, as shown below. (Anticipated Testimony of Dr. Channick.) Claims 9 and 10, however, require a statistically significant improvement in FVC after weeks 8, 12, or 16. (Anticipated Testimony of Dr. Channick.) The data in Tables 1-3 and Table 10 do not show any significant improvement in absolute or percent predicted FVC when compared to the treatment group baseline, only a difference between treated and placebo. (Anticipated Testimony of Dr. Channick.)

809. Dr. Wertheim and UTC are of the opinion that even if a statistically significant increase in both absolute and percent predicted FVC were required to provide adequate written description for claims 9 and 10 of the '327 patent, a patentee is not required to describe known inoperable embodiments of their invention and it would not be difficult for a POSA to determine which embodiments of the claims are operable and which are not. (Anticipated Testimony of Dr. Wertheim.) This opinion is based on the contention that a POSA would understand that if a particular patient population (e.g., PH-IIP), showed a statistically significant improvement in FVC, that would represent an operable embodiment of the claims, and vice versa. This position is an admission that the specification of the '327 patent does not provide written description support for the full scope of claims 9 and 10. (Anticipated Testimony of Dr. Channick.) If a POSA were to simply exclude inoperable embodiments, a POSA would eliminate, as inoperable, absolute FVC from claim 9 (1/2 the claim) and absolute FVC from claim 10 (which is expressly absolute FVC



represented by values in mL). (Anticipated Testimony of Dr. Channick.) Thus, there is no operable embodiment within the scope of claim 10 under Dr. Wertheim's view. (Anticipated Testimony of Dr. Channick.) It also would require a POSA to limit claims 9 and 10 to only subpopulations of PH-ILD and exclude the entire scope of the PH-ILD population encompassed by the claims. (Anticipated Testimony of Dr. Channick.)

810. Based on the foregoing, a POSA would not conclude that the inventors were in possession of the full scope of the FVC requirements claimed in claims 9 and 10 and as such, there is no written description support for these claims. (Anticipated Testimony of Dr. Channick.)

## **XI. INVENTORSHIP**

811. The '327 patent is invalid because it fails to name at least one individual who contributed to the conception of claim 1 of the '327 patent and should have been a named inventor—Dr. Aaron Waxman.

812. UTC did not conceive of the idea of using Tyvaso to improve exercise capacity in PH-ILD patients. Rather, as discussed previously in Section V.B, many independent physicians were actively using Tyvaso for treatment of PH-ILD beginning soon after Tyvaso's original approval in 2009 and well before April 17, 2020. For example, Dr. Rajan Saggar testified that, between 2010 and 2016, he proposed to UTC a larger clinical study involving the use of Tyvaso to treat PH-ILD patients, and that the idea to study treprostinil in PH-ILD was not UTC's idea. (Rajan Saggar Sept. 24 Depo. Tr. at 96:22-98:23; Rajan Saggar Nov. 20 Depo. Tr.169:2-20.)

813. Additionally, Leigh Peterson and Peter Smith, had no role in the INCREASE trial clinical protocol and consequently no role in the conception of the invention claimed by the '327 patent. The '327 patent specification makes clear that the INCREASE study is its foundation. Further, UTC has admitted that "[t]he INCREASE study ... forms the basis for the specification

of the '327 patent.” (April 23, 2024 Hearing Tr. at 8:7-10.) Leigh Peterson and Peter Smith have not contributed to the conception of the idea of using Tyvaso to improve exercise capacity in PH-ILD patients nor have they come up with the idea of the INCREASE study – they merely applied their ordinary skill in administering the INCREASE study.

**A. Dr. Aaron Waxman Clearly Contributed to the Conception of Claim 1 but was Improperly Omitted as an Inventor of the '327 Patent**

814. The '327 patent improperly omitted at least Dr. Aaron Waxman as an inventor, despite clear evidence that Dr. Waxman conceived of at least claim 1 of the '327 patent. For example, Dr. Waxman testified that he came up with the idea of treating Group 3 patients with inhaled treprostinil and that such a treatment ought to be studied:

Q. So if I understand correctly, patients, looking at this sentence, patients in Group-3 who were on inhaled treprostinil at Brigham & Women's for some period of time prior to 2014, you had their medical records available to you, is that right?

A. They were our patients, so yes, we had the medical records.

Q. And in doing this retrospective assessment, did you look at those medical records to aggregate the data that's reflected in the abstract?

A. Yes.

Q. Why did you think you should be studying inhaled treprostinil prior to 2014 in Group-3 patients?

A. Because I felt there was a significant unmet need.

Q. So why not try a different drug other than inhaled treprostinil to try to meet this need?

A. Well, again, I hypothesized that an inhaled approach would be better than a systemic approach.

Q. Did you come up with that idea? Was that an idea that you had?

A. At the Brigham it was certainly me. I don't know if I was the only person who came up with that idea.

(Waxman Depo. Tr. at 46:6-47:22 (objections omitted).)

**1. UTC Internal Documents Show Dr. Waxman Contributed to Conception of Claim 1**

815. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

816. [REDACTED]

[REDACTED]

[REDACTED], Allison Lim, a UTC employee, sent a same-day email stating:

Thank you so much for your time in allowing us to speak with you this morning regarding the use of Tyvaso in WHO Group 3 PH. I have attached the articles discussed this morning and summarized our plan of action below for your reference. *I will be in touch shortly to schedule a follow-up meeting with Dr. Waxman and colleagues and look forward to speaking with you further on this topic.*

(DTX0285, UTC\_LIQ00159920 at UTC\_LIQ00159920 (emphasis added).)

817. [REDACTED] a March 9, 2015 presentation by Dr. Waxman’s research group, titled “Inhaled Treprostinil in Group-3 Pulmonary Hypertension.” (DTX0385, Waxman 2015 Presentation at UTC\_PH-ILD\_082486.) The Waxman 2015 Presentation discusses a “[r]etrospective analysis of data” from “35 patients treated with iTre for 6 months,” and adds that the patients “[a]ll started on 3-breaths 4x daily and increased to a goal of 9-12 breaths 4x daily as tolerated.” (*Id.* at UTC\_PH-ILD\_082490.)

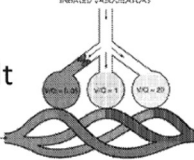
818. As discussed in Section D.4. above, the Waxman 2015 Presentation also indicates that the patients in this retrospective study were treated with Tyvaso, as Tyvaso was the only inhaled treprostinil therapy on the market in 2015. (Anticipated testimony of Dr. Hill.) The treatment regimen is also the same as the dosing claimed in the ’327 patent and encompasses the approved dosing regimen in the Tyvaso label for PAH. It further shows that the patients in this

retrospective study had a baseline mPAP above 24 mmHg and thus were above the mPAP needed to classify patients as having PH.

819. In addition to the data in the Waxman 2015 Presentation, it explains the motivation to pursue a study of inhaled treprostinil therapy in Group 3 PH patients. At the time of this presentation and as explained in the “Rational[e]” slide below, POSAs in the field believed that inhaled vasodilators, like Tyvaso, were less likely to cause V/Q mismatch in patients with PH-ILD than systemic vasodilators, because the inhaled treprostinil is selectively targeted to healthier areas of the lung that can participate in gas exchange.

### Rational for Inhaled Therapy

- Treatment with systemic pulmonary vasodilators may result in worsening V/Q imbalance.
- Inhaled therapy is delivered directly to well ventilated lung units preserving V/Q, and reducing undesirable alterations in perfusion
- Potential for increased efficacy and decreased systemic side effects



BRIGHAM AND WOMEN'S HOSPITAL HARVARD MEDICAL SCHOOL

820. Specifically, Dr. Waxman’s 2015 Presentation suggests that “[i]nhaled therapy is delivered directly to well ventilated lung units preserving V/Q, and reducing undesirable alterations in perfusion.” (*Id.* at UTC\_PH-ILD\_082489.) Therefore, Dr. Waxman was aware of the potential for V/Q imbalance with parenteral treprostinil, and thus conducted a retrospective study to investigate inhaled treprostinil therapy, specifically Tyvaso, in Group 3 PH patients. (Anticipated testimony of Dr. Hill.)

821. As also discussed above, Dr. Waxman's analysis saw a statistically significant increase in WHO functional class ( $p = 0.011$ ) and a statistically significant increase in mean six-minute walk distance ( $p = 0.0019$ ) at six months of treatment. (DTX0385, Waxman 2015 Presentation at UTC\_PH-ILD\_082498, -501.) Accordingly, Dr. Waxman's study demonstrated a statistically significant improvement in exercise ability for Group 3 PH patients, including PH-ILD patients.

822. The Waxman 2015 Presentation characterized these improvements as "Significant Improvement in WHO FC" and "Significant Improvement in 6-MWD[.]" (*Id.* at UTC\_PH-ILD\_082511.) Based on this data, the Waxman 2015 Presentation concluded that "[t]he findings of this pilot study provide preliminary evidence supporting the treatment of pre-capillary PAH in patients with advanced lung disease[.]" (*Id.* at UTC\_PH-ILD\_082512.) Dr. Waxman's conclusion supports that Dr. Waxman conceived of the method of improving exercise capacity in PH-ILD patients using inhaled treprostinil recited in claim 1 of the '327 patent, analyzed the retrospective data of the study he conducted using Tyvaso to collect data supporting his new method of treatment, and suggested further study in this area based on these results. (Anticipated testimony of Dr. Hill.)

823. Dr. Waxman testified that his intent in providing the abstract and presenting this data to UTC was "to convince them to do a clinical trial." (Waxman Depo. Tr. at 128:19-129:9.) Dr. Waxman testified that, after the presentation, he recalled Roger Jeffs, President of UTC, saying that "we're going to do this study." (*Id.* at 131:15-132:14.) Dr. Waxman testified that the INCREASE clinical trial was the ultimate endpoint of his efforts to convince UTC to do a Phase III clinical study in this Group III, PH-ILD patient population. (*Id.*)

824. These presentations and Dr. Waxman's testimony about this presentation support my opinion that UTC did not conceive the claimed method of improving exercise capacity in PH-ILD patients with Tyvaso or the corresponding INCREASE study. Instead, these presentations and communications demonstrate that Dr. Waxman, independent of UTC, conceived these ideas.

**2. Public Documents [REDACTED] Confirm Dr. Waxman Contributed to Claim 1 of the '327 Patent**

825. Dr. Waxman's November 15, 2017 letter to the FDA supporting UTC's Orphan Drug Designation application, Dr. Waxman indeed represented that his work "*has laid the basis for [the INCREASE trial's] concepts*" and that "as we have seen in our preliminary studies, it is anticipated that patients with ILD-PH may be more likely to benefit from prostacyclin therapy such as treprostinil." (DTX0281, UTC\_LIQ00104555 at -555, -556 (emphasis added).)

826. Dr. Peter Smith is a named inventor of the '327 patent and UTC corporate witness. Dr. Smith testified that "in 2015 there was some data ... that was shared in the form of a retrospective chart review done by Aaron Waxman at Brigham and Women's looking at a set of patients who had broad Group 3 pulmonary hypertension who were treated with inhaled treprostinil, and that was the *conception of the idea for the INCREASE study*." (Smith Depo. Tr. at 48:5-17 (emphasis added).) Dr. Smith confirmed that this data was from the Waxman 2015 Presentation. (*See id.* at 118:5-119:6.) Dr. Smith also testified that other UTC employees, Gil Golden, Prakash Sista, CQ Deng, and Leigh Peterson, also "indicated that [Dr. Waxman's study] was essentially *the conception of the idea*" to investigate Tyvaso for the improvement of exercise capacity in PH-ILD patients. (*Id.* at 49:8-16 (emphasis added).)

827. Dr. Waxman also testified that he was the head of the INCREASE study's steering committee and that he participated in the design of the INCREASE study protocol, including dosing and the inclusion and exclusion criteria of the study. (Waxman Depo. Tr. at 132:12-133:2,

143:1-144:22.) Regarding his motivation for conducting his retrospective study, which is described in Agarwal 2015 and Faria-Urbina 2018, and ultimately proposing the INCREASE study to UTC, Dr. Waxman testified that he treated PH-ILD patients with inhaled treprostinil at Brigham & Women's Hospital because he "thought that we should be studying [the treatment method]" and that he "felt there was a significant unmet need." (Waxman Depo. Tr. at 46:6-47:22.) Dr. Waxman added that it was his idea that "an inhaled approach would be better than a systemic approach" when it comes to the treatment of PH-ILD patients with treprostinil. (*Id.*)

828. The Agarwal 2015 and Faria-Urbina 2018 publications also support that Dr. Waxman conceived of the method of improving exercise capacity in PH-ILD patients using inhaled treprostinil. Both studies retrospectively analyzed data of Group 3 PH patients who were treated with inhaled treprostinil. (*See* DTX0137, Agarwal 2015; DTX0348, Faria-Urbina 2018.) Both studies report inhaled treprostinil treatment of those patients according to the dosing regimen disclosed in the Tyvaso label, which is now the same dosing for PH-ILD as well as the dosing used in the INCREASE study, and the patients exhibited statistically significant improvements in six-minute walk distance. (D0137, Agarwal 2015; DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_9939.) Finally, Agarwal 2015 and Faria-Urbina 2018 both call for further study of inhaled treprostinil in Group 3 PH patients. (D0137, Agarwal 2015; DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_9941.) To the extent that UTC alleges that Dr. Waxman's contributions to claim 1 of the '327 patent were in the prior art literature, and thus could not be the basis for joint inventorship, this argument is flawed. It is unclear how this supports that Dr. Waxman is not an inventor, because both Agarwal 2015 and Faria-Urbina 2018 are Dr. Waxman's publications. Thus, while in the prior art, they evidence his conception and reduction to practice.

829. Based on the above, Dr. Waxman's work formed the basis for the INCREASE study and that he conceived of the method of treatment of at least claim 1 of the '327 patent, which discloses the same patient population and dosing as the INCREASE study, and therefore should have been a named inventor on the '327 patent. Therefore, the '327 patent is invalid for failure to name Dr. Waxman as an inventor on the '327 patent.

**3. Dr. Waxman's conception of the method of treatment was sufficiently definite and permanent**

830. UTC may argue that Dr. Waxman's use of inhaled treprostinil to treat PH-ILD patients was merely experimental, hypothesis-generating, and merited further investigation. But Dr. Waxman's method of using inhaled treprostinil to treat PH-ILD patients to improve exercise capacity was already definite and permanent prior to 2015 when Agarwal 2015 was published and certainly by 2018 when Faria-Urbina 2018 was published and was not "experimental." Indeed, Dr. Waxman testified that he treated these patients prospectively and continued to treat additional patients, as he described in his 2017 John Vane symposium presentation. (*See* Waxman Depo. Tr. at 83:5-84:1; DTX0140, 2017 Waxman Tr. at 9:4-7.) Even if Dr. Waxman's treatment of PH-ILD patients with inhaled treprostinil prior to 2015 was experimental, hypothesis-generating, and merited further investigation," that does not change the fact that Dr. Waxman conceived of using inhaled treprostinil to treat PH-ILD patients to improve their exercise capacity well before the April 2020 filing date of the '810 application leading to the '327 patent. It also does not change the fact that, as reported in Faria Urbina, these PH-ILD patients actually improved their exercise capacity and in fact, did so in a statistically significant manner. (*See* DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009936; DTX0505, Faria-Urbina 2018 Supplementary Materials at UTC\_PH-ILD\_219377-378.)



831. Dr. Waxman's conception of this method of treatment prior to the publication of Agarwal 2015 was already definite and permanent because Dr. Waxman actually practiced the method to treat PH-ILD patients according to the dosing regimen of the Tyvaso label, which is the same as the dosing regimen disclosed in the '327 patent, and in fact saw a statistically significant improvement in 6MWD. (DTX0344, Agarwal 2015 at UTC\_PH-ILD\_009828.) UTC cannot dispute that Dr. Waxman indeed used the method of treatment and saw positive results in PH-ILD patients, facts they recognized when they invited Dr. Waxman, in 2015, to present his findings.

832. Dr. Waxman's conception and reduction to practice is also reflected in his 2017 John Vane symposium presentation. Dr. Waxman stated in his 2017 presentation that "[a]ll of the patients were started in the usual way, on inhaled treprostinil, with – starting with three breaths four times daily and increased over time to an initial goal of 9 to 12," that they have "treated more than 60 patients" with this regimen, and that "[p]atients with [PH-ILD] had upwards of a 65-meter improvement and patients with combined pulmonary fibrosis emphysema ... still walked a significantly greater distance of around 28 to 30 meters." (DTX0140, 2017 Waxman Tr. at 9:10-10:1, 10:11-14, 13:17-14:3; Waxman Depo. Tr. at 80:23-84:1, 86:22-87:7.) Dr. Waxman's conception and reduction to practice is also shown in Faria-Urbina 2018, which also shows treatment according to the claimed method of treatment and statistically significant improvement in 6MWD. (DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937-938; DTX0505, Faria-Urbina 2018 Supplementary Materials at UTC\_PH-ILD\_219377-378.) These two references further show that Dr. Waxman had a definite and permanent idea of the method of treatment and had reduced it to practice prior to April 2019.

833. No further "research" or "experimentation" was needed because even after concluding the INCREASE trial, UTC did not change the method of treatment, *i.e.*, the dosing

regimen, in the 2021 Tyvaso label, which added PH-ILD, to be any different from that disclosed in the 2009 Tyvaso label and used by Dr. Waxman in Agarwal 2015. (Waxman Depo. Tr. at 207:14-210:19; *compare* DTX0357, 2009 Tyvaso® Label (UTC\_PH-ILD\_010692), with DTX0360, 2021 Tyvaso® Label (UTC\_PH-ILD\_010744); *see also* Tapson Depo. Tr. at 39:10-43:14, 45:18-49:14, 55:11-60:4, 62:4-63:2; Smith Depo. Tr. at 223:8-233:10; Waxman Depo. Tr. at 223:17-24.) Thus, the INCREASE trial merely corroborated Dr. Waxman's conception and reduction to practice.

834. A comparison of the 2009 Tyvaso label, Agarwal 2015, Faria-Urbina 2018, the INCREASE study protocol, and the 2021 Tyvaso label shows that the methods of treatment disclosed by each reference is the same, even after the randomized, placebo-controlled INCREASE trial:

Source	Indication / Treatment Population	Method of Treatment
2009 Tyvaso label <sup>8</sup>	PAH	<ul style="list-style-type: none"> <li>• Single breath of Tyvaso delivers approximately 6 mcg of treprostinil.</li> <li>• Initial dosage: 3 breaths (18 mcg) per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths.</li> <li>• Administer in 4 separate treatment sessions each day, approximately 4 hours apart.</li> <li>• Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated.</li> <li>• Titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated.</li> </ul>
Agarwal 2015 <sup>9</sup>	35 WHO Group 3 patients including PH-ILD patients	<ul style="list-style-type: none"> <li>• Treatment with inhaled treprostinil for 6 months.</li> </ul>

<sup>8</sup> DTX0357, 2009 Tyvaso® Label at UTC\_PH-ILD\_01063.

<sup>9</sup> DTX0344, Agarwal 2015 at UTC\_PH-ILD\_009828.

		<ul style="list-style-type: none"> <li>All patients started on 3 breaths, 4 times daily and increased to a goal of 9-12 breaths 4 times daily as tolerated.</li> </ul>
Faria-Urbina 2018 <sup>10</sup>	22 WHO Group 3 patients / 9 PH-ILD patients	<ul style="list-style-type: none"> <li>Patients received inhaled treprostinil at three breaths (18 µg) four times daily (72 µg/day).</li> <li>Inhaled treprostinil doses were increased as tolerated by three additional breaths (18 µg) per dosing session every 3-7 days to achieve a dose of at least 9-12 breaths or more (≥54 µg) four times daily (≥216 µg/day).</li> </ul>
INCREASE Study Protocol Amendment 3 <sup>11</sup>	Approx. 314 subjects at approx. 120 centers	<ul style="list-style-type: none"> <li>Patients treated with inhaled treprostinil (6 mcg/breath) or placebo</li> <li>All subjects will initiate inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) 4 times daily (during waking hours)</li> <li>Study drug doses should be maximized throughout the study, dose escalations (additional 1 breath 4 times daily) can occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily, as clinically tolerated.</li> </ul>
2021 Tyvaso label <sup>12</sup>	PAH and PH-ILD	<ul style="list-style-type: none"> <li>Single breath of Tyvaso delivers approximately 6 mcg of treprostinil.</li> <li>Initial dosage: 3 breaths (18 mcg) per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths.</li> <li>Administer in 4 separate treatment sessions each day, approximately 4 hours apart (during waking hours).</li> <li>Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated.</li> <li>Titrate to target maintenance doses of 9 to 12 breaths per treatment session, 4 times daily.</li> </ul>

<sup>10</sup> DTX0348, Faria-Urbina 2018 at UTC\_PH-ILD\_009937.

<sup>11</sup> DTX0401, INCREASE Study Protocol Amendment 3 (UTC\_PH-ILD\_105083) at UTC\_PH-ILD\_105087-90.

<sup>12</sup> DTX0360, 2021 Tyvaso® Label at UTC\_PH-ILD\_010744.

835. UTC may contend that more than minor modifications were required to transform Dr. Waxman's idea into a successful clinical trial using an administration method that provides physicians and patients with an intended and expected improvement in exercise capacity in PH-ILD patients. However, this is flawed analysis of comparing Dr. Waxman's work to the INCREASE trial instead of the '327 patent claims. Additionally, even if the INCREASE trial protocol were the conception for the claims, [REDACTED] [REDACTED]. (Peterson Depo. Tr. at 45:5-24; Smith Depo. Tr. at 129:16-131:5, 147:12-148:24.) [REDACTED] [REDACTED] (Deng Depo. Tr. at 16:20-17:23.) [REDACTED] [REDACTED] [REDACTED] [REDACTED] (Id. at 56:4-58:5.)

836. The only differences between the disclosed treatment regimen of Agarwal 2015 and the INCREASE study protocol are in the patient population—Agarwal 2015 included a broader range of WHO Group 3 patients while the INCREASE study was more narrowly focused on PH-ILD patients. Claim 1 of the '327 patent, from which all the other claims depend, merely recites in relevant part “improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease[.]” ('327 patent at Claim 1.) The claims include *all types* of PH-ILD patients, including those in Agarwal 2015, Faria-Urbina 2018, and INCREASE.

837. Furthermore, even after the INCREASE study, the 2021 Tyvaso label was not limited to the specific patient population included in the INCREASE trial. (*See generally* DTX0360, 2021 Tyvaso® Label (UTC\_PH-ILD\_010744).) Given that any supposed patient

population limitation in the INCREASE study did not make its way into the 2021 Tyvaso label, Dr. Waxman's method of treatment, as presented in Agarwal 2015 and at least Faria-Urbina 2018, was already definite and permanent as of their conception prior to April 2020.

#### **4. Scientific certainty is not needed for inventorship**

838. UTC may contend that because Agarwal 2015 and Faria-Urbina 2018 were uncontrolled, retrospective studies, they could not provide "scientific certainty" regarding the efficacy of the method of treatment. But there is no support for the contention that "scientific certainty" is required for conception. Rather, this seems to apply to reduction to practice, which is not needed to be considered an inventor. Nonetheless, for the reasons above, Dr. Waxman both conceived and reduced the invention to practice before April 2020.

839. UTC may point to multiple "failed" trials to support its claim. However, the failed trials, with the exception of the PERFECT study, all involve *non-treprostinil* drugs, and, as such, they would not contribute to the "general industry skepticism" for the use of *treprostinil* drugs for the treatment of PH-ILD. Dr. Waxman agrees. He was specifically asked about the studies looking into drugs other than treprostinil for the treatment of PH-ILD and testified that they do not show skepticism, but instead would reflect "narrow-minded[ness]" from "conservative physicians" who would not "deviate from the guidelines[.]" (Waxman Depo. Tr. at 226:4-17.) Also, the PERFECT study was for COPD, not PH-ILD, which is the subject matter of the '327 patent claims. (See DTX0604, Steven D. Nathan et al., *Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results*, 63 Eur. Respir. J. (2024), <https://pmc.ncbi.nlm.nih.gov/articles/PMC11154754/pdf/ERJ-00172-2024.pdf>.)

B. [REDACTED]  
[REDACTED]

840. [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

841. The final amendment of the INCREASE study protocol is dated February 15, 2017.  
(See DTX0401, UTC\_PH-ILD\_105083.) [REDACTED]  
[REDACTED] (Deng Depo. Tr. at 15:11-20; Smith Depo. Tr. at  
20:12-22:12; Peterson Depo. Tr. at 22:13-17.)

842. [REDACTED]  
[REDACTED] (Peterson Depo. Tr. at 83:6-18.)  
[REDACTED]  
[REDACTED] (Peterson Depo. Tr. at 61:23-62:17) a [REDACTED]  
[REDACTED] *Id.* at 83:6-18).

843. [REDACTED]  
[REDACTED]  
[REDACTED] (Smith Depo. Tr. at 46:19-47:11.) [REDACTED]  
[REDACTED]  
[REDACTED] (*Id.* at 91:1-15.) [REDACTED]  
[REDACTED] (Deng Depo. Tr. at 74:9-22.)

844. [REDACTED]  
[REDACTED]

[REDACTED]

[REDACTED] (Laliberte Depo. Tr. at 117:15-120:25, 122:4-21, 123:4-14, 125:5-12.)

845. [REDACTED]

[REDACTED] (Deng Depo. Tr. at 138:16-139:6.) [REDACTED]

[REDACTED]

[REDACTED] (Deng Depo. Tr. at 156:6-

157:6.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

846. UTC may contend that “scientific certainty” was needed in order for an inventor to conceive of a definite and permanent idea of the invention. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (Anticipated testimony of Dr. Hill.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **XII. INEQUITABLE CONDUCT**

847. The Asserted Claims of the '327 patent are unenforceable due to inequitable conduct of [REDACTED]

[REDACTED]

A. [REDACTED]

848. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]

849. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

850. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

851. Mr. Snader was involved in the preparation of a letter, submitted by UTC to the FDA on February 12, 2024, which identified the '793 and the '327 patents as at least two of the patents covering the PH-ILD indication for Tyvaso. (DTX0028, LIQ\_PH-ILD\_00000847; Snader Depo. Tr. 229:19-237:2.)

**B. The References Which [REDACTED] Failed to Disclose Were Material to the Prosecution of the '327 Patent**

852. The following undisclosed references (collectively referred to as the “Undisclosed References”) were material to the prosecution of the '327 patent: (1) the Court’s opinion in the previous District Court litigation, including its claim construction regarding the meaning of “pulmonary hypertension,” (2) Dr. Hill’s District Court trial testimony, (3) the Federal Circuit’s affirmance of the District Court’s decision (numbers (1)-(3) collectively referred to as “District Court Documents”), (4) UTC’s Patent Owner Response submitted in the '793 IPR (“’793 POR”), (5) the '793 IPR declaration of Dr. Aaron Waxman submitted in support of UTC’s Patent Owner Response, (6) the PTAB’s Final Written Decision (“FWD”) invalidating the '793 patent, and (7) the Federal Circuit’s opinion affirming the PTAB’s FWD (numbers (4)-(7) collectively referred to as “’793 IPR Documents”). (Anticipated Testimony of Dr. Hill.)

853. None of the materials already before the Examiner during the prosecution of the '327 patent are cumulative to the Undisclosed References, nor do any of the materials already before the Examiner describe the scope of the '793 patent claims. (Anticipated Testimony of Dr. Hill.) The Undisclosed References establish that the claims of the '793 patent cover the same PH-

ILD subject matter as the claims of the '327 patent, which makes the Undisclosed References material. (Anticipated Testimony of Dr. Hill.)

854. UTC takes the position that a POSA would understand the '793 patent: *fails* to disclose patients with PH-ILD (it discloses a “different patient class”); *fails* to disclose “administration of treprostinil to improve exercise capacity in a patient having PH-ILD”; *fails* to disclose claims directed to PH-ILD; and *fails* to disclose “a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease.” Dr. Nathan testified, however, that the claims of the '793 patent are not directed to improving exercise capacity in PH-ILD patients. (3/10/24 Nathan Depo. Tr. 250:23-251:24, 252:17-253:14, 254:19-25.) If Dr. Nathan and UTC are correct, then the Examiner, purportedly considering the '793 patent from the perspective of a POSA, would reach the same conclusion during prosecution of the '327 patent. (Anticipated Testimony of Dr. Hill.) As discussed herein, the Undisclosed References establish, contrary to the position UTC has taken, that the '793 patent discloses patients with PH-ILD, the administration of treprostinil to improve exercise capacity in a patient having PH-ILD, and a method of improving exercise capacity in a patient having PH-ILD. Thus, the Undisclosed References are material as they provide the full scope and context of the '793 patent.

855. The '793 IPR Documents confirm that UTC understood the '793 patent to encompass improving exercise capacity in PH-ILD patients—a key fact that was absent from any of the materials before the Examiner. The '793 POR and Mr. Maebius's testimony confirm that the arguments he and ████████ made in the '793 POR are directed to the '793 patent claims. (See DTX0007, '793 POR (LIQ\_PH-ILD\_00000110) at LIQ\_PH-ILD\_00000180-181; Maebius Depo. Tr. at 43:17-46:17, 137:3-18.) It is also confirmed by the letter UTC submitted to the FDA, reviewed beforehand by Mr. Snader, specifically informing the FDA that the claims of the '793

patent cover the “new [PH-ILD] indication” on the FDA label. (*See* DTX0028, Feb. 12, 2024, FDA Letter (LIQ\_PH-ILD\_00000847) at LIQ\_PH-ILD\_00000852; Snader Depo. Tr. at 229:19-237:19.)

856. Further, as confirmed by Mr. Maebius, the claims of the ’793 patent are directed to improving the exercise capacity of PH-ILD patients. (*See* Maebius Depo. Tr. at 136:1-137:18.) Specifically, in the ’793 POR, Mr. Maebius and [REDACTED] argued that the claims of the ’793 patent satisfied a long-felt but unmet need for this exact indication by stating that “[i]nhaled treprostinil is currently approved for [PAH] and [PH-ILD].” (DTX0007, ’793 POR at LIQ\_PH-ILD\_00000180.) To make this argument, Mr. Maebius and [REDACTED] submitted the 2021 version of the Tyvaso label, which includes the FDA approved PH-ILD indication directed to improving exercise capacity. (Maebius Depo. Tr. at 136:1-137:18.) When asked about this statement in the ’793 POR, Mr. Maebius confirmed that it would inform the Examiner that the ’793 patent claims cover the PH-ILD indication on the Tyvaso label, which specifically states: “Tyvaso is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.” (*See id.* at 137:3-18; DTX0360, 2021 Tyvaso® Label at UTC\_PH-ILD\_010745.) These representations leave no doubt that Mr. Maebius and [REDACTED] argued that a POSA would understand that the ’793 patent claims cover improving exercise capacity in PH-ILD patients.

857. In arguing that the ’793 IPR Documents are cumulative of the ’793 patent, Dr. Nathan states that it is “clear from the face of the ’793 patent itself” that the ’793 patent “cover[s] methods of treating PH-ILD.” (Anticipated Testimony of Dr. Nathan.) Dr. Nathan testified, however, that the claims of the ’793 patent are not directed to improving exercise capacity in PH-ILD patients. (3/10/24 Nathan Depo. Tr. 250:23-251:24, 252:17-253:14, 254:19-25.) Thus,

according to Dr. Nathan, a POSA, which would include the examiner reviewing the '327 patent, would understand the '793 patent claims to *not* cover the same subject matter as the '327 patent claims. The fact that [REDACTED] and Mr. Maebius told the PTAB in the '793 POR the exact opposite, further establishes the materiality of the '793 IPR documents.

858. Dr. Nathan also argues that because Liquidia's petition for IPR was before the Examiner, by definition, the Final Written Decision is substantively duplicative. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan appears to argue that by disclosing a select document from the IPR, the Examiner would somehow have knowledge of other relevant documents in the IPR. But this would not be possible. (Anticipated Testimony of Dr. Nathan.) The positions taken in an IPR petition represent the arguments of the challenging party, not a determination of the claims' actual scope. The IPR petition also does not include [REDACTED] Mr. Maebius's statements refuting the petition. In contrast, the Final Written Decision reflects the PTAB's independent analysis and ultimate ruling on the scope of the '793 patent claims. It does not make sense that a single document from one party to an IPR would be cumulative of either argument made in an opposing party's submission and arguments and rationale set-forth by the PTAB in its FWD. (Anticipated Testimony of Dr. Hill.) The Examiner was entitled to consider not just Liquidia's arguments, but also the PTAB's findings. Thus, the Final Written Decision is not cumulative of Liquidia's IPR petition but instead provides material conclusions that the Examiner never had an opportunity to review.

859. The District Court Documents confirm that the claims of the '793 patent cover treating patients with PH-ILD. (Anticipated Testimony of Dr. Hill.)

860. On June 4, 2020, before the '327 patent application was filed, UTC filed a complaint against Liquidia in the United States District Court for the District of Delaware.

(DTX0666, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 1:20-cv-755-RGA-JLH, D.I. 1 (D. Del. June 4, 2020).) UTC amended this complaint to further assert that Liquidia infringed its '793 patent on July 22, 2020. (DTX0667, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 1:20-cv-755-RGA-JLH, D.I. 16 (D. Del. July 22, 2020).)

861. The Court's opinion in the District Court litigation includes its claim construction regarding the meaning of "pulmonary hypertension" in the '327 patent claims. The District Court concluded that based on the specification of the '793 patent, the scope of "treating pulmonary hypertension" in claim 1 includes "treating all five Groups of PH." (DTX0036, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 1:20-cv-755-RGA-JLH, D.I. 433 at 38 (D. Del. Aug. 31, 2022) ("District Court Opinion"); *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 464 (D. Del. 2022), *aff'd*, 74 F.4th 1360 (Fed. Cir. 2023).)

862. The District Court trial concerning the '793 patent took place in March 2022 and the District Court issued its opinion in August 2022. (*Id.*) The opinion was issued during the prosecution of the '327 patent application and prior to [REDACTED] amendment to the pending claims of the '327 patent covering interstitial lung disease.

863. During the district court trial, Dr. Hill provided testimony regarding the meaning of "pulmonary hypertension" in the claims of the '793 patent: "[p]ulmonary hypertension' as used, as far as I can tell in the patent, and would be used as a general term by a POSA comprises all the five different groups. It refers to . . . any condition where . . . there's an elevation of the pulmonary pressure, pulmonary pressures." (DTX0076, LIQ\_PH-ILD\_00101296 at LIQ\_PH-ILD\_00101298.) Dr. Hill further testified that, in column 1 line 41 of the '793 patent, "the first sentence says that pulmonary hypertension may occur due to various reasons, and the different entities of pulmonary hypertension were classified, based on clinical and pathological grounds, in

five categories according to the latest WHO convention.” (*Id.*) Dr. Hill also noted that the pulmonary hypertension patients described in Example 1 of the ’793 patent included patients in pulmonary hypertension Group 3, which includes patients with interstitial lung disease. (*Id.*)

864. Given that the “treating pulmonary hypertension” term in the ’793 patent claims was found to cover methods of treating all Groups of PH, including WHO Group 3 PH which includes interstitial lung disease, the proceedings before the District Court and its issued Opinion were material to the prosecution of the ’327 patent claims, specifically with reference to the ’793 patent, which cover treating pulmonary hypertension associated with interstitial lung disease. Specifically, claim 1 was amended on May 10, 2023 during the prosecution of the ’327 patent to read as indicated below:

Claim 1: (Currently Amended) A method of improving exercise capacity in a patient having treating a pulmonary hypertension associated with interstitial lung disease due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises an amount of at least 6 micrograms per breath.

(DTX0334, ’327 patent file history at UTC\_PH-ILD\_009739.)

865. Additionally, it is clear that Mr. Snader also believed that the ’793 patent covers the same approved indication of treating PH-ILD which is covered by at least claim 1 of the ’793 patent, based on a letter from UTC submitted to the FDA on February 12, 2024, stating the following:

During the pendency of the 30-month stay for the PAH indication, ***UTC received approval of the new PH-ILD indication.*** Supplement Approval, NDA 22387/s-017 (Mar. 31, 2021). In July 2023, Liquidia—fully aware of FDA’s Bundling Rule—decided to amend the YUTREPIA 505(b)(2) NDA instead of submitting a new 505(b)(2) NDA to add the PH-ILD indication. In that amendment, Liquidia certified

to the Orange Book patent information for TYVASO, and UTC timely sued Liquidia for patent infringement, but *the subsequent litigation on the patents covering the new indication—the '793 patent, and U.S. Patent No. 11,826,327 ("the '327 patent")*—did not trigger a 30-month stay because those patents were added to the Orange Book for TYVASO after the January 20, 2020 submission of the original YUTREPIA 505(b)(2) NDA. According to the Liquidia Letter, the amendment contained no additional data.

(DTX0028, LIQ\_PH-ILD\_00000847 at LIQ\_PH-ILD\_00000852 (emphasis added); *see also* Snader Depo. Tr. at 229:19-237:2.)

866. This passage makes clear that Mr. Snader believed that both the '327 patent *and* the '793 patent covered the PH-ILD indication for Tyvaso. Mr. Snader testified during his deposition in this case that he was involved in the preparation of this letter. (Snader Depo. Tr. at 229:19-231:9.) [REDACTED]

[REDACTED]

867. Despite this knowledge, neither the District Court's claim construction nor Dr. Hill's trial testimony were submitted during the prosecution of the '327 patent. These documents, including the Federal Circuit's affirmance, were material to the prosecution of the '327 patent claims and should have been submitted because they would have made clear to the Examiner that the method of treating pulmonary hypertension in the '793 patent covers the '327 patent claimed method of improving exercise capacity in PH-ILD as recited in claim 1 as indicated below. These documents provide valuable context as to the scope and meaning of the '793 patent claims as encompassing treating PH-ILD patients. (Anticipated Testimony of Dr. Hill.) Had the USPTO been provided the District Court's claim construction and Dr. Hill's trial testimony, that would have formed the basis to render at least claim 1 of the '327 patent unpatentable based on the '793 patent alone, or in combination with prior art cited by the USPTO during prosecution. (Anticipated Testimony of Dr. Hill.) For that reason, the District Court Documents are material references, which should have been disclosed to the USPTO during the prosecution of the '327 patent.



868. The District Court Documents are not cumulative of information disclosed in Agarwal 2015, WO 2008/098196 (“Wade”), WO 2016/205202 (“Zhang”), and WO 2015/138423 (“Malinin”) (collectively, the “Four Prior Art References”), which were considered during the prosecution of the ’327 patent. (Anticipated Testimony of Dr. Hill.) The Four Prior Art References do not provide the necessary context to understand the full scope of the ’793 patent. (Anticipated Testimony of Dr. Hill.)

869. The District Court Documents confirm that the claims of the ’793 patent cover treating patients with PH-ILD. (Anticipated Testimony of Dr. Hill.) Dr. Nathan, UTC expert witness, argues that Agarwal 2015 does not treat PH-ILD patients because the PH is “out of proportion” to ILD. (Anticipated Testimony of Dr. Nathan.) Thus, UTC has taken the position that Agarwal 2015 is not directed to PH-ILD. Therefore, the District Court Documents, which establish that the claims of the ’793 patent cover the same PH-ILD subject matter as the claims of the ’327 patent, are not cumulative to Agarwal 2015 based on this position. (Anticipated Testimony of Dr. Hill.)

870. Dr. Nathan, UTC expert witness, argues that Agarwal 2015 does not treat PH-ILD patients because the PH is “out of proportion” to ILD. (Anticipated Testimony of Dr. Nathan.) Thus, UTC has taken the position that Agarwal 2015 is not directed to PH-ILD. Therefore, the District Court Documents, which establish that the claims of the ’793 patent cover the same PH-ILD subject matter as the claims of the ’327 patent, are not cumulative to Agarwal 2015 based on this position. (Anticipated Testimony of Dr. Hill.)

871. Dr. Nathan also alleges various deficiencies in Agarwal 2015, including that it “does not disclose or calculate the dosage of treprostinil/breath[.]” does not separate the data for PH-ILD patients from other Group 3 PH patients, and lacks a “placebo group for comparison,”

which limits its predictive power. (Anticipated Testimony of Dr. Nathan.) He further argues that because the patient population in Agarwal 2015 included patients with obstructive, restrictive, and mixed obstructive/restrictive disease, it is impossible to determine what the effects of treprostinil treatment were specifically for PH-ILD. (*Id.*) If Agarwal 2015 lacks the necessary specificity and reliability to provide meaningful conclusions about treating PH-ILD patients (it does not), then it also cannot serve as a basis for arguing that the District Court Documents are cumulative. The District Court Documents make clear that the '793 patent claims cover treating patients with PH-ILD. (Anticipated Testimony of Dr. Hill.) Agarwal 2015 does not discuss the scope of '793 patent. (Anticipated Testimony of Dr. Hill.) Because Agarwal 2015 says nothing about the '793 patent, the District Court Documents provide new, material disclosures that are not cumulative of Agarwal 2015. (Anticipated Testimony of Dr. Hill.)

872. Dr. Nathan also argues that the District Court Documents are cumulative of the prior art documents—Wade, Zhang, and Malinin—cited by the Examiner in the March 6, 2023 rejection because, according to Dr. Nathan, they describe “‘treat[ing]’ PH-ILD with treprostinil.” (Anticipated Testimony of Dr. Nathan.)

873. Dr. Nathan alleges that because the Examiner reviewed Wade and nevertheless permitted the '327 patent to issue, the District Court Documents are cumulative. (Anticipated Testimony of Dr. Nathan.) Dr. Nathan ignores the arguments that Mr. Maebius [REDACTED] made to the Examiner about Wade during prosecution. During prosecution, [REDACTED] and Mr. Maebius argued that “Wade does not teach or suggest ‘a single administration event that comprises at least 6 micrograms per breath’ as amended claim 1 [of the '327 patent] recites.” (*See* DTX0334, '327 patent file history at UTC\_PH-ILD\_009743.) Based on this argument, the Examiner allowed the '327 patent claims. (*Id.*) The '793 patent, on the other hand, discloses this

limitation by describing delivering 15 mcg of treprostinil as a single administration event (“single event dose”) in 1, 2, or 3 breaths. (Anticipated Testimony of Dr. Hill.) Dr. Nathan admitted that the claims of the ’793 patent disclose the same dosing as claim 1 of the ’327 patent. (3/28/25 Nathan Depo. Tr. 198:14-199:1, 268:5-21.) And had the District Court Documents been submitted to the Examiner, the Examiner would have known that the ’793 patent claims, which include PH-ILD patients, do disclose the very limitations Mr. Maebius [REDACTED] alleged were lacking in Wade, thereby the District Court Documents are not cumulative to Wade. (Anticipated Testimony of Dr. Hill.)

874. Dr. Nathan criticizes Wade for failing to demonstrate the intended or expected improvement of the Asserted Claims because it provides no data on the effects of inhaled Tyvaso on exercise capacity in patients with PH-ILD. (Anticipated Testimony of Dr. Nathan.) But when discussing inequitable conduct, Dr. Nathan relies on Wade as supposedly containing sufficient information to make the District Court Documents cumulative. (Anticipated Testimony of Dr. Nathan.) If Wade is insufficient to show efficacy in PH-ILD patients, then it cannot also serve as a basis for dismissing the materiality of the District Court Documents. Wade does not provide any information about the scope of the ’793 patent’s claims, whereas the District Court Documents explicitly establish that the ’793 patent covers treating PH-ILD patients. (Anticipated Testimony of Dr. Hill.) Accordingly, Wade does not render the District Court Documents cumulative. (Anticipated Testimony of Dr. Hill.)

875. During prosecution, [REDACTED] Mr. Maebius argued that “[Zhang] teaches nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breath . . . [and that Zhang] teaches nothing regarding improving exercise capacity in any patient.” (DTX0334, ’327 patent file history at UTC\_PH-ILD\_009743.) The District Court

Documents establish the '793 patent discloses all these limitations. (Anticipated Testimony of Dr. Hill.) Specifically, because the District Court Documents confirm that the claims of the '793 patent include treating PH-ILD patients, they establish that the '793 patent and its claims disclose the alleged missing elements from Zhang, including treprostinil doses, inhaled treprostinil, and improvements in PH-ILD patients. (Anticipated Testimony of Dr. Hill.) The District Court Documents are not cumulative of the information disclosed in Zhang. (Anticipated Testimony of Dr. Hill.) Additionally, Zhang does not contain any information regarding the scope of the '793 patent's claims, whereas the District Court Documents do. (Anticipated Testimony of Dr. Hill.)

876. During prosecution, [REDACTED] Mr. Maebius argued that "Malinin teaches nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breath." (DTX0334, '327 patent file history at UTC\_PH-ILD\_009743.) For the reasons discussed above with respect to Zhang, the District Court Documents are not cumulative to Malinin. (Anticipated Testimony of Dr. Hill.) Additionally, like Wade and Zhang, Malinin does not contain any information regarding the scope of the '793 patent claims. (Anticipated Testimony of Dr. Hill.) Thus, the District Court Documents are not cumulative of the information disclosed in Malinin. (Anticipated Testimony of Dr. Hill.)

877. For the purposes of arguing a lack of materiality, Dr. Nathan admits that the '793 patent covers a method of treating patients with PH-ILD, stating that this is clear from the face of the '793 patent itself. (Anticipated Testimony of Dr. Nathan.) However, in both his declaration in support of UTC's preliminary injunction ("PI Declaration") and in his Rebuttal Report, Dr. Nathan argues that the '793 patent does not disclose a method of improving exercise capacity in PH-ILD patients. (*See* DTX0625, D.I. 28 (Nathan PI Decl.) at ¶ 176; Nathan Rebuttal at ¶ 553; *see also* Nathan PI Depo. Tr. at 250:23-254:25.) Dr. Nathan's opinion completely undercuts his

argument that the '793 IPR Documents are cumulative to the '793 patent itself. The inconsistent positions taken by UTC underscores the materiality of the '793 IPR Documents.

878. UTC has argued the Undisclosed Documents are cumulative to the '793 patent because the specification of the '327 patent incorporates the '793 patent by reference. (Anticipated Testimony of Dr. Nathan.) The '327 patent only references the '793 patent in the context of disclosing a type of inhalation delivery device. Specifically, the specification states: “Pulsed inhalation devices are disclosed, for example, in U.S. patent application publication No. 20080200449, U.S. Pat. Nos. 9,358,240; 9,339,507; 10,376,525; and 10,716,793, each of which is incorporated herein by reference in its entirety.” ('327 patent at 20:53-57.) This selective reference underscores the materiality of the Undisclosed References, as the '793 patent was only mentioned in the '327 patent in the context of pulsed inhalation devices and not for the fact that the '793 patent and its claims are directed to the same subject matter as the '327 patent claims. (Anticipated Testimony of Dr. Hill.)

879. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] In other words, UTC has taken the position that the '793 patent and its claims are *not* directed to PH-ILD patients, but instead a “different patient class,” and *not* directed to improving the exercise capacity of PH-ILD patients.

880. [REDACTED]

[REDACTED]

[REDACTED]

**C. The Single Most Reasonable Inference to be Drawn is that [REDACTED] Withheld the Undisclosed References with the Specific Intent to Deceive the USPTO**

881. The single most reasonable inference to be drawn is that [REDACTED] withheld the Undisclosed References with the specific intent to deceive the USPTO.

882. Despite knowing that material information must be disclosed and despite submitting three IDSs, [REDACTED] intentionally failed to submit or otherwise notify the Examiner about the Undisclosed References.

883. On May 10, 2023, [REDACTED] amended the '327 patent claims to overcome prior art rejections to recite: "improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease." (DTX0334, '327 patent file history, Applicant's Amendment and Remarks at UTC\_PH-ILD\_009743-45.) In view of this amendment, as well as their participation in and knowledge of the '793 IPR and the '793 patent district court case, as well as actual rejections made during prosecution and the amendments and arguments made to overcome those rejections, [REDACTED], knew or should have known, that Undisclosed References provide context with respect to the disclosure of the '793 patent, including the fact that the '793 patent claims do cover improving exercise capacity in PH-ILD patients. [REDACTED] knew or should have known that had they disclosed the Undisclosed References, the Examiner would have relied on the '793 patent to reject the amended claims of the '327 patent. In particular, [REDACTED], intentionally withheld this information from the Examiner because this information makes clear that the '793 patent claims the same subject matter as the '327 patent and directly refutes the

arguments made concerning the alleged deficiencies of the cited prior art. Further in view of [REDACTED] knowledge of the positions taken concerning the scope of the '793 patent claims to cover interstitial lung disease, the most reasonable inference to be drawn is that [REDACTED] intentionally withheld the Undisclosed References with an intent to deceive the PTO and obtain allowance of the '327 patent.

884. [REDACTED] did not disclose that on November 10, 2021, prior to the above amendment to the pending '327 patent claims, they submitted arguments to the PTAB during the '793 patent IPR asserting that the '793 patent fulfilled a long-felt need of providing treatment to those with interstitial lung disease and in particular, covered the PH-ILD indication in the Tyvaso label, the same subject matter as the '327 patent. In view of the actual rejections made during prosecution and the amendments and arguments made to overcome those rejections, [REDACTED], knew or should have known that bringing the '793 patent to the specific attention of the Examiner, coupled with the arguments submitted during the '793 patent IPR, would have resulted in further anticipatory, obviousness and double patenting rejections. Being intimately involved in the '793 patent IPR and the arguments submitted therein, and with knowledge of the amendments made to the pending '327 patent claims, the most reasonable inference to be drawn is that [REDACTED], intentionally withheld the arguments made concerning the scope of the '793 patent claims during the '793 patent IPR with an intent to deceive the PTO and obtain allowance of the '327 patent.

885. [REDACTED] did not disclose any of the following, all of which are material to the '327 patent: (1) that prior to the above amendment to the pending '327 patent claims, UTC argued, and Liquidia's expert, Dr. Hill testified, that the '793 patent claims cover all 5 PH Groups, which would include patients with interstitial lung disease; (2) that on August 31,

2022, prior to the above amendment to the pending '327 patent claims, the District Court issued its Opinion determining the '793 patent claims cover all 5 PH Groups, which would include interstitial lung disease; or (3) that on July 24, 2023, prior to the issuance of the '327 patent claims, the Federal Circuit affirmed the District Court's Opinion that the '793 patent claims included all 5 PH Groups, which would include interstitial lung disease. In view of the actual rejections made during prosecution and the amendments and arguments made to overcome those rejections, [REDACTED], knew or should have known that bringing the '793 IPR submissions, Institution Decision, and FWD to the specific attention of the Examiner, coupled with UTC and Liquidia's submissions to the District Court, the District Court's Opinion and the Federal Circuit's affirmance thereof, would have resulted in further anticipatory, obviousness and double patenting rejections. Furthermore, [REDACTED] was aware of Dr. Rothblatt's 2018 statements disclosing the use of inhaled treprostinil to treat pulmonary hypertension associated with interstitial lung disease and knew that they were material to prosecution of the '327 patent.

886. [REDACTED]ader had motivation to withhold this material information from the PTO because of the value a patent directed to PH-ILD would have to UTC. For instance, prior to issuance of the '327 patent, [REDACTED] knew that the '793 patent, which they told the PTAB covered improving exercise capacity in PH-ILD patients, was in an instituted IPR and had been invalidated by the PTAB in the '793 IPR. Thus, [REDACTED] knew that UTC no longer possessed a patent that included claims covering the new Tyvaso PH-ILD indication. [REDACTED] also knew, prior to issuance of the '327 patent, that Liquidia had filed an amendment to add an indication to the Yutrepia label directed to improving exercise capacity in PH-ILD patients. Thus, both [REDACTED] had motivation to



obtain additional patents with claims that specifically covered improving exercise capacity in PH-ILD patients.

887. The value of a PH-ILD indication, and protecting it, was well known within UTC.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

888. Each claim of the '327 patent is drawn to improving exercise capacity in patients with interstitial lung disease. [REDACTED] had specific knowledge and actually advocated to the PTAB that the '793 patent disclosed this same subject matter. [REDACTED], also possessed specific knowledge of UTC and Liquidia's submissions to the District Court and the District Court's decision as affirmed by the Federal Circuit, that determined that the '793 patent claims covered all 5 PAH Groups, which includes interstitial lung disease—the same subject matter of the '327 patent. [REDACTED] knew this information filled the gaps of the alleged deficiencies of the prior art cited during prosecution. Accordingly, [REDACTED], had a duty to bring to the Examiner's attention the related '793 patent litigation and IPR submissions to the PTO during prosecution of the '327 patent.

889. [REDACTED] intentional withholding of material information constituted a breach of the duty of candor owed to the USPTO with a specific intent to deceive and constitutes inequitable conduct that renders all of the claims of the '327 patent unenforceable.

# EXHIBIT 4

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff,

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

C.A. No. 23-00975-RGA-SRF

**EXHIBIT 4: PLAINTIFF'S STATEMENT OF CONTESTED ISSUES OF LAW**

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## **I. INTRODUCTION**

In accordance with Local Rule 16.3(c)(5) of the Local Rules of Civil Practice and Procedure of the United States District Court for the District of Delaware, Plaintiff United Therapeutics Corporation (“Plaintiff” or “UTC”) submits the following statement of contested issues of law for the action against Defendant Liquidia Technologies, Inc. (“Defendant” or “Liquidia”).

The following statements are not exhaustive, and Plaintiff reserves the right to prove any matters identified in its pleadings, interrogatory responses, and/or expert reports, or as otherwise required to maintain the ’327 patent as valid and prove that it is infringed. Plaintiff reserves the right to modify or amend this Exhibit to the extent necessary to reflect any future rulings by the Court, to supplement or amend this Exhibit to fairly respond to any new issues that Defendant may raise, to address any additional discovery produced by Defendant, to address any amendments to Defendant’s NDA, or as otherwise justified. To the extent Plaintiff’s issues of fact that remain to be litigated, which is submitted as Exhibit 2 hereto, contains issues of law, those issues are incorporated herein by reference. Moreover, if any issue of law identified below should properly be considered an issue of fact, then such statement should be considered to be part of Plaintiff’s statement of issues of fact that remain to be litigated.

Further, Plaintiff’s identification of the issues that remain to be litigated on issues where Defendant bears the burden of proof is based on its understanding of the arguments that Defendant has put forth to date and relevant legal presumptions. To the extent Defendant attempts to introduce different or additional legal arguments to meet its burden of proof, or seeks to rebut any legal presumptions, Plaintiff reserves its rights to contest those legal arguments, and to present any and all rebuttal evidence in response to those arguments, and will not be bound by this summary of



remaining legal issues.

**A. The '327 Patent**

**1. The Asserted Patent and Claims**

1. The Patent-in-Suit and asserted claims are:

U.S. Patent No.	Asserted Claims
11,826,327 ( “the '327 patent”)	1–11 and 14–19

2. The '327 patent issued on November 28, 2023 from U.S. Patent Application No. 17/233,061 (“the '061 application”), filed on April 16, 2021. The '061 application claims priority to U.S. Provisional Patent Application No. 63/011,810 (“the '810 Provisional”), filed on April 17, 2020, and U.S. Provisional Patent Application No. 63/160,611 (“the '611 Provisional”), filed on March 12, 2021.

**2. Priority Date**

3. At least claims 1-2, 6-11, and 14-16 of the '327 patent are entitled to claim the benefit of the April 17, 2020 filing date of the '810 Provisional.

**3. Inventorship**

4. The named inventors of the '327 patent are Leigh Peterson, Peter Smith, and Chunqin Deng.

5. The named inventors of the '327 patent are the correct inventors.

**4. Person of Ordinary Skill in the Art**

6. Claim terms “are examined through the viewing glass of a person skilled in the art.” *Ferguson Beauregard/Logic Controls, Div. of Dover Res., Inc. v. Mega Systems, LLC*, 350 F.3d 1327, 1338 (Fed. Cir. 2003).

7. “Factors that may be considered in determining level of ordinary skill in the art

include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.” *Env’t Designs, Ltd. v. Union Oil Co. of California*, 713 F.2d 693, 696 (Fed. Cir. 1983).

8. The POSA is often part of a team with other scientists and clinicians. *See e.g., Astellas Pharma Inc. v. Lupin Ltd.*, No. CV 23-819-JFB-CJB, 2024 WL 4626225, at \*4 (D. Del. Oct. 30, 2024) (“[The scope of the patent] is best understood by a multidisciplinary team that understands both the science of drug absorption and the clinical context for the problem.”); *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 597 (D. Del. 2018), *aff’d sub nom., Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019) (“[T]he Court finds that a person of ordinary skill in the art would be a person or team of persons with a degree or degrees in the relevant fields such as chemistry, biology, pharmaceuticals, or medicine[.]”). Testimony is also helpful where the witness “has technical expertise on a relevant aspect of the pertinent art.” *Sanofi v. Glenmark Pharms. Inc., USA*, No. CV 14-264-RGA, 2016 WL 10957311, at \*1 (D. Del. May 12, 2016).

9. The definition of a POSA should not exclude inventors. *OrthoPediatrics Corp. v. Wishbone Med., Inc.*, No. 3:20-CV-929 JD, 2022 WL 4978169, at \*5 (N.D. Ind. Oct. 4, 2022) (“While both inventors would seem to qualify under the Plaintiff’s more experience-focused POSITA definition, the available evidence would not readily suggest that they would qualify under the Defendants’ definition. *See Daiichi*, 501 F.3d at 1256 (indicating that looking at the patent inventors’ qualifications and experience can help a court settle on a POSITA definition). The narrowness of the Defendants’ proposed qualification requirement therefore leads the Court to find that the Defendants’ proposed definition falls short.” (citing *Daiichi Sankyo Co v. Apotex, Inc.*,

501 F.3d 1254, 1256 (Fed. Cir. 2007)); *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1347 (Fed. Cir. 2000) (“The district court should not have constructed the hypothetical person of ordinary skill in the art by determining which persons working in the field of the invention are likely to be familiar with the relevant literature. Instead, the court should have considered the educational level of the inventor; the type of problems encountered in the art; the prior art solutions to those problems; the rapidity with which innovations are made; the sophistication of the technology, and the educational level of workers in the field.”).

10. A POSA may rely on other experts. *McCoy v. Heal Sys., LLC*, 850 F. App'x 785, 788 (Fed. Cir. 2021).

11. Biostatisticians, even those not explicitly meeting the POSA definition, possess the technical expertise to opine from the POSA’s perspective on “relevant aspect[s] of the pertinent art,” e.g., “how a POSA would interpret and react to post-hoc analyses of clinical trial data,” especially when the opposing party puts that aspect “squarely in issue.” *Sanofi*, 2016 WL 10957311, at \*1-2, \*1 n.3 (crediting the expert for having “taught medical students how to interpret clinical trial data for over 20 years and [having] personal knowledge of the statistics-based curricula offered by other medical schools.”). Further, biostatisticians “who [are] regularly consulted by members of research teams evaluating drug-treatment efficacy” possess relevant expertise even if they do not meet proposed POSA definitions. *Novartis AG v. Actavis Elizabeth LLC*, C.A. No. 14–1487–LPS, 2017 WL 1398347, at \*1 (D. Del. Apr. 17, 2017).

12. In assessing whether an expert can qualify as a POSA, the court in *Kyocera* did not consider “the extent to which a person of ordinary skill in the art may rely on the testimony or information supplied by others in reaching conclusions as to infringement or invalidity.” *Kyocera Senco Indus. Tools Inc. v. Int’l Trade Comm’n*, 22 F.4th 1369, 1376-78, 1378 n.6 (Fed. Cir. 2022)

(noting that the definition of POSA was unchallenged on appeal); *see GeigTech E. Bay LLC v. Lutron Elecs. Co., Inc.*, No. 18 Civ. 05290 (CM), 2023 WL 6614486, at \*32 (S.D.N.Y. Sept. 20, 2023) (finding “a sufficient relationship between [the expert’s] significant relevant technical expertise and the [claimed] technology ... for [the expert] to offer his opinions as a [POSA].”) In applying *Kyocera*, a lack of experience may be cured by reliance on another expert in developing their opinions. *Bial-Portela & CA. S.A. v. Alkem Lab’ys. Ltd.*, Civ. No. 18-304-CFC-CJB, 2022 WL 4244989, at \*7 (D. Del. Sept. 15, 2022) (raising this potential solution when excluding a non-clinician expert who only lacked experience treating the relevant patients or prescribing the relevant drug).

13. The Federal Circuit permits expert testimony on issues that must be viewed from the POSA’s perspective—even from those lacking certain expertise in the art—if the “testimony [at issue] establishe[s] an adequate relationship between [the expert’s] experience and the claimed invention.” *SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010) (permitting an expert to testify as to infringement and acknowledging the testimony was limited to the expert’s relevant expertise).

#### **B. Defendant’s Accused Infringing Product**

14. The accused infringing product is that described in Defendant’s New Drug Application No. 213005 and an amendment thereto, submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and pursuant to 21 U.S.C. § 355(b)(2) (the “505(b)(2) Application”), to the U.S. Food and Drug Administration (“FDA”) seeking approval to engage in the commercial manufacture, use, or sale of YUTREPIA™ (treprostinil) for the treatment of pulmonary hypertension associated with interstitial lung disease (“PH-ILD”) to improve exercise ability (“Proposed Product”).

## II. CLAIM CONSTRUCTION

### A. Legal Standards

15. Claim construction is an issue of law that is reserved for the court to determine. *Markman v Westview Instruments, Inc.*, 517 U.S. 370, 372, 391 (1996). Proper claim construction of a patent's claims requires review of the patent's intrinsic evidence and, when appropriate, extrinsic evidence. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313–14 (Fed. Cir. 2005). The intrinsic evidence to be considered includes the claims, specification, and prosecution history. *Id.* at 1314–17. When intrinsic evidence is unable to provide a clear construction, courts may use extrinsic evidence to assist in the interpretation including relevant scientific principles, the meaning of technical terms, the state of the art, dictionaries, treatises, and inventor and expert testimony. *See id.* at 1317–18, 1324. The intrinsic, and if necessary extrinsic, evidence is used to give the claims their ordinary and customary meaning that the POSA, at the time of the invention, would have interpreted the terms to mean. *Id.* at 1313–14. Of note, the practice of using dictionary definitions, a form of extrinsic evidence, is generally disfavored for construing individual parts of a component claim, especially if the specification provides its own definition. *See Align Tech., Inc. v. 3Shape*, No. CV 17-1648-LPS, 2021 WL 2320139, at \*12 (D. Del. June 7, 2021). And any “expert testimony at odds with the intrinsic evidence must be disregarded.” *Network Com., Inc. v. Microsoft Corp.*, 422 F.3d 1353, 1361 (Fed. Cir. 2005).

16. Claim construction is to interpret the claims to cover both “what the inventors actually invented and intended to envelop with the claim.” *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). Because patents are given a presumption of validity by 35 U.S.C. § 282, claim construction should act to preserve the claims' validity, except in cases where an invalidating construction would be the “only claim construction that is consistent with

the claim’s language and the written description.” *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999). A patent’s specification “is always highly relevant to a claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). “The court must always read the claims in view of the full specification.” *SanDisk Corp. v. Memorex Prod., Inc.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005). Further, any claim construction that excludes a preferred embodiment “is rarely, if ever, correct.” *Vitronics*, 90 F.3d at 1583; *see also, e.g., SanDisk*, 415 F.3d at 1285; *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 865 (Fed. Cir. 2004); *CUPP Computing AS v. Trend Micro Inc.*, 53 F.4th 1376, 1381 (Fed. Cir. 2022) (“We require ‘highly persuasive’ evidence to read claims as excluding a preferred embodiment of the invention.”); *Otsuka Pharm. Co. v. Lupin Ltd.*, No. CV 21-900-RGA, 2022 WL 2952759, at \*2 (D. Del. July 26, 2022) (“[A] claim interpretation that would exclude the inventor’s device is rarely the correct interpretation”). Additionally, there is “a heavy presumption that claim terms carry their full ordinary and customary meaning, unless it can [be] show[n] th[at] patentee expressly relinquished claim scope.” *See Epistar Corp. v. Int’l Trade Comm’n*, 566 F.3d 1321, 1334–37 (Fed. Cir. 2009).

17. During the claim construction phase of this case, culminating in an August 29, 2024, joint claim construction brief, the parties proposed construction of four terms, one agreed and three disputed. Following the Markman hearing, the Court adopted the parties’ agreed construction for the preamble of claim 1 and adopted constructions for the three disputed terms, as shown below.

Term	Construction
“A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease”  ’327 patent, claim 1	This preamble is limiting, as agreed by the parties

Term	Construction
<p>“a”/“the” in the following terms:</p> <p>“a patient,” “the patient,” “a maximum tolerated dose,” “a single administration event,” “the administering,” and “the single inhalation administration event”</p> <p>’327 patent, claims 1-5, 8-10, and 15-19</p>	<p>“one or more”</p>
<p>“maximum tolerated dose”</p> <p>’327 patent, claim 1</p>	<p>plain and ordinary meaning; not indefinite</p>
<p>“pulsed inhalation device”</p> <p>’327 patent, claims 11 and 14</p>	<p>“a device that provides for non-continuous inhaled drug delivery”</p>

D.I. 155.

18. As identified in the table above, the preamble of claim 1 is limiting. *See Allergan*, 935 F.3d at 1374-76; *Sanofi v. Lupin Atlantis Holdings S.A.*, 2016 WL 5842327, at \*2–3 (D. Del. Oct. 3, 2016); *Forest Labs., LLC v. Apotex Corp.*, 2016 WL 6645784, at \*1 n.5 (D. Del. Nov. 8, 2016); *Sanofi Mature IP v. Mylan Labs. Ltd.*, 757 F. App’x 988 (Fed. Cir. 2019) (preamble limiting when giving “intentional purpose ... for which the method must be performed”).

19. Claim 1 requires, among other things, a method step of “administering.” During claim construction, Liquidia did not propose any constructions to add a requirement for “measuring,” such as measuring by physicians. Nor did Liquidia seek to add requirements for the steps of administering to a group, measuring outcomes, aggregating results, and performing statistical analysis. The claims do not require physicians to perform those steps for there to be infringement. *See Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306, 354 (D. Del. 2020), *aff’d sub nom. Bristol-Myers Squibb Co. v. Sigmapharm Lab’ys, LLC*, 858 F. App’x 359 (Fed. Cir. 2021) (rejecting argument that claim limitation reciting particle size in a pharmaceutical composition required the particle size to be measured, noting that “the Court

understands the particle size limitation to describe a feature of the claimed invention, not a measurement requirement.”).

20. Many courts have recognized that “a” means one or more unless the context dictates otherwise. *See, e.g., ABS Glob., Inc. v. Cytonome/St, LLC*, 84 F.4th 1034, 1040 (Fed. Cir. 2023) (“[U]se of ‘a’ . . . before a noun naming an object requires that the phrase be construed to mean ‘one or more’ unless the context sufficiently indicates otherwise.” (quotation omitted)); *Lite-Netics, LLC v. Nu Tsai Cap. LLC*, 60 F.4th 1335, 1345 (Fed. Cir. 2023) (same); *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000) (“This court has repeatedly emphasized that an indefinite article ‘a’ . . . in patent parlance carries the meaning of ‘one or more’ in open-ended claims containing the transitional phrase ‘comprising.’”); *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008) (“That ‘a’ . . . can mean ‘one or more’ is best described as a rule, rather than merely as a presumption or even a convention.”); *Azurity Pharms., Inc. v. Alkem Lab’ys Ltd.*, No. CV 19-2100-LPS, 2021 WL 5332406, at \*3 (D. Del. Nov. 16, 2021) (“As a general rule, the word[] ‘a’ . . . in a patent claim carr[ies] the meaning of ‘one or more.’”); *01 Communique Lab’y, Inc. v. LogMeIn, Inc.*, 687 F.3d 1292, 1297 (Fed. Cir. 2012) (same). Further, “[t]he exceptions to this rule are extremely limited: a patentee must evince a clear intent to limit ‘a’ or ‘an’ to ‘one.’” *01 Communique Lab’y*, 687 F.3d at 1297 (quoting *Baldwin*, 512 F.3d at 1342).

21. Courts “normally do not interpret claim terms in a way that excludes disclosed examples in the specification.” *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1305 (Fed. Cir. 2007) (rejecting proposed claim interpretation that would exclude disclosed examples in the specification); *see also Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276–77 (Fed. Cir. 2008) (collecting cases and describing precedent as “finding district court’s claim construction



erroneously excluded an embodiment described in an example in the specification, where the prosecution history showed no . . . disavowal of claim scope”); *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1369 (Fed. Cir. 2003) (finding district court's claim construction erroneously excluded an embodiment described in an example in the specification, where the prosecution history showed no such disavowal of claim scope); *Osram GmbH v. Int’l Trade Comm’n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (rejecting claim construction that “would exclude the . . . products that the patents were designed to cover”). And, “[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction.” *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004) (internal quotations omitted).

22. Further, there is a ““general proposition [that] a limitation that does not exist in a claim should not be read into that claim.”” *Pfizer Inc. v. Alkem Lab’ys. Ltd.*, No. CV 13-1110-GMS, 2014 WL 12798743, at \*1 n.1 (D. Del. Dec. 2, 2014) (quoting *Biovail Corp. Int’l v. Andrx Pharms., Inc.*, 239 F.3d 1297, 1301 (Fed. Cir. 2001)).

23. A claim element has patentable weight when it calls for a “manipulative difference.” *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001); see *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1374-79 (Fed. Cir. 2019). A claim element calls for a manipulative difference when it changes or affects how the method is performed. *In re Copaxone Consolidated Cases*, 906 F. 3d 1013, 1023 (Fed. Cir. 2018).

24. A dependent claim possesses patentable weight—even if it describes a specified result—if that dependent claim is exclusively directed to the result specified in that particular claim. *L’Oréal USA, Inc. v. Olaplex, Inc.*, 844 Fed. Appx. 308, 324 (Fed. Cir. 2021) (explaining

that such claims “limit the options covered by the subject matter defined by the claims on which they depend to options that produce the concretely specified results—thus making a difference in the manipulative steps”); *see also id.* at 324 (“[T]o treat the limitations as of no legal effect would be to interpret each of these dependent claims as entirely a nullity. The fairer understanding of these claims is that they limit the options covered by the subject matter defined by the claims . . . .”).

**B. Contested Issued of Law**

25. As raised in Defendant’s pending *Daubert* motion regarding Drs. Nathan and Thisted, whether the dependent limitations of claims 2-11 and 14-19 of the ’327 patent have patentable weight. *See, e.g.*, D.I. 283.

26. As raised in Defendant’s pending *Daubert* motion regarding Drs. Nathan and Thisted, whether claims 2-10 and 17-19 of the ’327 patent require a patient or healthcare provider to take a measurement and/or perform statistical analysis. *See, e.g.*, D.I. 283.

27. As raised in Defendant’s pending Motion *in Limine* No. 1, whether the term “pulmonary hypertension associated with interstitial lung disease” (“PH-ILD”) incorporates patients with “out of proportion” or “severe” pulmonary hypertension as set forth in Defendant’s Motion *in Limine*.

28. As raised in Defendant’s pending Motion *in Limine* No. 2, whether the term “forced vital capacity” (“FVC”), as used in claim 9, must encompass both absolute FVC and percent predicted FVC.

29. As raised in Defendant’s pending *Daubert* motion regarding Dr. Wertheim, whether the 20 mL improvement in forced vital capacity required by claim 10 of the ’327 patent must be statistically significant. *See, e.g.*, D.I. 281.

### III. INFRINGEMENT

#### A. Legal Standards

30. Infringement is a question of fact. *Eli Lilly & Co. v. Teva Parenteral Meds.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017). Plaintiff has the burden of proving infringement by a preponderance of the evidence. *Id.*; *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1314 (Fed. Cir. 2011).

31. “A patentee may prove infringement by any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient[.]” *Martek BioSciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) (internal quotation marks omitted) (citing *Forest Labs. v. Abbott Labs.*, 239 F.3d 1305, 1312 (Fed. Cir. 2001)); *Liquidia Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1219 (Fed. Cir. 2006).

#### 1. Infringement in the Hatch-Waxman Context

32. A § 271(e)(2)(A) infringement suit differs from typical infringement suits (e.g., a § 271(a) infringement suit) in that infringement inquiries “are hypothetical because the allegedly infringing product has not yet been marketed.” *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003); see *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570 (Fed. Cir. 1997) (“The relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product.”). Patentees in Hatch-Waxman litigations asserting method patents do “not need to prove an actual past instance of direct infringement by a physician to establish infringement under 35 U.S.C. § 271(e)(2)(A).” *Vanda Pharms. v. West-Ward Pharms.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018).

33. In a Hatch-Waxman Act suit, the infringement inquiry is a hypothetical inquiry because it is conducted and determined prior to any actual marketing, sale, or use of one or more

generic proposed drug products based upon an analysis of the proposed generic product and administration instructions that the accused infringer is likely to sell and provide following FDA approval. *Abbott Labs. v. Torpharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002) (the “infringement inquiry ... is focused on the product that is likely to be sold following FDA approval ... [b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the [NDA]’s description of the drug”); *cf. Novartis Corp. v. Ben Venue Labs.*, 271 F.3d 1043, 1045, 1047 (Fed. Cir. 2001).

34. To prove infringement, the patentee need only show that it is more likely than not that the proposed NDA product would, if commercially marketed, satisfy the claim limitations of at least one of the claims of the patents-in-suit. *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1287 (Fed. Cir. 2010); *Abbott Labs.*, 300 F.3d at 1373.

35. In determining whether a proposed NDA product would more likely than not infringe at least one claim of at least one of the patents-in-suit, a court must consider all relevant evidence, including the NDA filing itself and other evidence provided by the parties. *Adams*, 616 F.3d at 1287. As stated above, any evidence may be considered, including circumstantial evidence.

36. As to patents claiming new methods of treatment, a § 505(b)(2) NDA applicant may still be liable for inducing infringement even though it does not directly infringe a method patent. 35 U.S.C. § 271(b).

## **2. Infringement Under the Doctrine of Equivalents**

37. A party that makes, uses, sells, offers to sell within, or imports into the United States a product (and/or by a process) that does not literally meet all of the elements of a claim and thus does not literally infringe that claim, can still directly infringe if that product (and/or that process) satisfies the claim elements “under the doctrine of equivalents.” *Warner-Jenkinson Co. v. Hilton*

*Davis Chem. Co.*, 520 U.S. 17, 21 (1997) (“Under this doctrine, a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is ‘equivalence’ between the elements of the accused product or process and the claimed elements of the patented invention.”).

38. Under the doctrine of equivalents, a product or process infringes a claim if the accused product or process contains elements or performs steps that literally meet or are equivalent to each and every element of the claim. *Warner-Jenkinson*, 520 U.S. at 40. An element or step is equivalent to an element of a claim that is not met literally if a person having ordinary skill in the field of technology of the patent would have considered the differences between them to be “insubstantial” or would have found that the structure or action: (1) performs substantially the same function and (2) works in substantially the same way (3) to achieve substantially the same result as the element of the claim. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950). In order to prove infringement by “equivalents,” the patentee must prove the equivalency of the structure or action to the claim element by a preponderance of the evidence. *Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1282 (Fed. Cir. 2011). Each element of a claim must be met by the accused product or process either literally or under the doctrine of equivalents for the court to find infringement. *Seal-Flex, Inc. v. Athletic Track & Ct. Const.*, 172 F.3d 836, 842 (Fed. Cir. 1999).

39. Known interchangeability of the claim element and the proposed equivalent is a factor that can support a finding of infringement under the doctrine of equivalents. *Warner-Jenkinson*, 520 U.S. at 36. In order for the structure or action to be considered interchangeable, the claim element must have been known at the time of the alleged infringement to a person having ordinary skill in the field of technology of the patent. *Id.* at 37.

### 3. Induced Infringement

40. 35 U.S.C. § 271(b) provides that “[w]hen one actively induces infringement of a patent, he may still be liable as an infringer.”

41. Direct infringement is a necessary predicate for a finding of induced infringement in ordinary patent infringement cases. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 921 (2014); *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961); *Eli Lilly*, 845 F.3d at 1363-64; *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (“Direct infringement under § 271(a) occurs where all steps of a claimed method are performed by or attributable to a single entity.”).

42. Inducement liability requires that “the defendant possessed specific intent to encourage another’s infringement and not merely that the defendant had knowledge of the acts alleged to constitute infringement.” *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (quoting *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990) (internal quotations omitted)); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010) (quotations omitted).

43. Circumstantial evidence can support a finding of specific intent to induce infringement. *AstraZeneca*, 633 F.3d at 1060 (citing *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir. 1988)); *i4i Ltd. Partnership v. Microsoft Corp.*, 598 F.3d 831, 851-52 (Fed. Cir. 2010) (holding instructions teaching the use of the product in an infringing manner constituted inducing infringement).

44. “Inducement can be found where there is ‘[e]vidence of active steps taken to encourage direct infringement,’ which can in turn be found in ‘advertising an infringing use or instructing how to engage in an infringing use.’” *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm.*

*Corp.*, 785 F.3d 625, 630–31 (Fed. Cir. 2015) (alteration in original) (quoting *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005)). To establish active inducement, a patent owner must show that the accused infringer had actual knowledge of the patent or was willfully blind to its existence. *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 764-66 (2011).

45. In the Hatch-Waxman context, “the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent . . . .” *Eli Lilly and Co. v. Actavis Elizabeth LLC*, 435 F. App’x 917, 926 (Fed. Cir. July 29, 2011); *see also Wyeth v. Sandoz*, 703 F. Supp. 2d 508, 521 (E.D.N.C. 2010) (“Evidence of ‘active steps taken to encourage direct infringement such as advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe.’” (quoting *Grokster*, 545 U.S. at 936 (quotations, citations, & alterations omitted))). When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians and patients taking the drug, “[t]he label must encourage, recommend, or promote infringement.” *Takeda*, 785 F.3d at 631; *AstraZeneca*, 633 F.3d at 1060; *Wyeth*, 703 F. Supp. 2d at 521.

46. “The contents of the label itself may permit the inference of specific intent to encourage, recommend, or promote infringement.” *Vanda Pharms.*, 887 F.3d at 1129 (citing *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017)).

47. Induced infringement can be proven where the instructions in a proposed label would lead at least some consumers (*e.g.*, patients and/or their instructing physicians) to practice a claimed method of a patent. *AstraZeneca*, 633 F.3d at 1060. The label “just need[s] to instruct doctors and patients to administer a single event dose that is therapeutically effective.” *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 462-63 (D. Del. 2022) (citing

*AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010)); *see also Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017).

48. A patentee in a Hatch-Waxman litigation asserting method patents does not have to prove that prior use of the NDA-approved drug satisfies the limitations of the asserted claims. *See, e.g., Sanofi*, 875 F.3d at 643 (affirming inducement finding where the district court found that “the inducing act will be the marketing by [ANDA applicants] of their generic dronedarone drugs with the label described” and “the induced act will be the administration of dronedarone by medical providers to patients meeting the criteria set forth in the [claims at issue]”); *Eli Lilly*, 845 F.3d at 1368 (“not requir[ing] evidence regarding the general prevalence of the induced activity”); *AstraZeneca*, 633 F.3d at 1057-60 (affirming district court’s grant of a preliminary injunction based on claims of induced infringement where the district court found that “the proposed label would cause some users to infringe the asserted method claims”); *see also Warner-Lambert*, 316 F.3d at 1364 (“The infringement case is therefore limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed.”).

49. Accordingly, Plaintiff “can satisfy its burden to prove the predicate direct infringement by showing that if the proposed [ ]NDA product were marketed, it would infringe the [asserted patents].” *Vanda*, 887 F.3d at 1130; *see, e.g., Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1401, 1408 (Fed. Cir. 2014) (“The infringement determination is thus based on consideration of all relevant evidence, and because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA’s description of the drug, the ANDA itself dominates the analysis.” (alterations and internal quotation marks omitted)); *AstraZeneca*, 633 F.3d at 1060 (explaining that the district court “correctly determined” that



language in the ANDA label “would inevitably lead some consumers to practice the claimed method”).

50. Even if the proposed § 505(b)(2) NDA product has “substantial noninfringing uses,” the § 505(b)(2) NDA applicant may still be liable for inducing infringement. *Vanda*, 887 F.3d at 1133 (“Section 271(b), on inducement, does not contain the ‘substantial noninfringing use’ restriction of section 271(c), on contributory infringement.” (quoting *Sanofi*, 875 F.3d at 646)). If a proposed drug label contains language that instructs, encourages, recommends, and/or promotes users to perform the patented method, even if the language may be applied to non-infringing uses, it will “inevitably lead some consumers to practice the claimed method.” *AstraZeneca*, 633 F.3d at 1060.

51. A label instructing or encouraging users to follow the instructions in an infringing manner is “sufficient even though some users would not follow the instructions.” *Eli Lilly*, 845 F.3d at 1368-69 (“[I]t is irrelevant that some users may ignore the warnings in the proposed label.”); *Sanofi*, 875 F.3d at 646 (“The content of the label in this case permits the inference of specific intent to encourage the infringing use.”); *AstraZeneca*, 633 F.3d at 1060; *Vanda Pharms.*, 887 F.3d at 1130-32 (affirming finding of induced infringement based on “recommend[ation]s” in the label that physicians perform the claimed steps, stating that “[e]ven if not every practitioner will prescribe an infringing dose, that the target dose range ‘instructs users to perform the patented method’ is sufficient to ‘provide evidence of [the ANDA filer’s] affirmative intent to induce infringement.’” (quoting *AstraZeneca*, 633 F.3d at 1060 (Fed. Cir. 2010))).

52. In Hatch-Waxman cases, the entire proposed label should be considered to determine whether it will induce infringement, and such a finding may be made when the patent claims are not identical to the language of the indication. *Braintree Labs., Inc. v. Breckenridge*

*Pharm., Inc.*, 688 F. App'x 905, 909-10 (Fed Cir. 2017) (finding induced infringement of claims requiring purgation, a step of colon cleansing, when the FDA-approved indication was for fully cleansing the colon: purgation is “not a distinct use” of the proposed generic product, but rather the “means by which the approved indication achieves its result”); *Vanda Pharms.*, 887 F.3d at 1131 (relying on language in the Pharmacokinetics section of the label to find that it recommends performing the patented method).

53. A factfinder may also consider evidence outside of an accused infringer's label in analyzing whether the defendant has sought to “encourage” an infringing use of a product. *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1336 (Fed. Cir. 2021).

54. Thus, “a person can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses[.]” *Vanda Pharms.*, 887 F.3d at 1133 (citing *Grokster*, 545 U.S. at 934–37).

55. Defendant cannot avoid induced infringement based on a purported subjective belief that it is “practicing the prior art” or that claims 1-11 and 14-19 are invalid. *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 643 (2015); *DeLorme Publ'g Co. v. ITC*, 805 F.3d 1328, 1332 (Fed. Cir. 2015) (“[A] good-faith belief in the patent's invalidity was not a defense to induced infringement.”).

56. For prescription drug products for which an NDA is submitted after June 20, 2006, the FDA requires the prescription drug labeling to meet certain labeling and content requirements. 21 C.F.R. § 201.56(b)(1). The Indications and Usage Section “must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.” 21 C.F.R. § 201.57(c)(2). The indication “must be

supported by substantial evidence of effectiveness based on adequate and well-controlled studies.” 21 C.F.R. § 201.57(c)(2)(iv). The Clinical Studies Section “must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results.” 21 C.F.R. § 201.57(c)(15).

#### **4. Willful Infringement**

57. “[T]he concept of ‘willfulness’ requires a [factfinder] to find no more than deliberate or intentional infringement.” *Eko Brands, LLC v. Adrian Rivera Maynez Enters., Inc.*, 946 F.3d 1367, 1378 (Fed. Cir. 2020). “Willful infringement is a question of fact ... .” *Polara Eng’g Inc v. Campbell Co.*, 894 F.3d 1339, 1353 (Fed. Cir. 2018).

58. “[T]he Federal Circuit [has] held that a patentee in a ANDA case can recover attorney fees for willful infringement/litigation misconduct under the appropriate circumstances.” *Novartis Pharms. Corp. v. Teva Pharms. USA, Inc.*, No. CIV.A.05-CV-1887, 2005 WL 3664014, at \*2 (D.N.J. Dec. 30, 2005) (citing *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1342 (Fed. Cir. 2000)).

59. The patentee must show infringement is willful by a preponderance of the evidence. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1339 (Fed. Cir. 2016).

60. A defendant “cannot insulate itself from liability for enhanced damages by creating an (ultimately unsuccessful) invalidity defense for trial after engaging in the culpable conduct of copying.” *Id.* at 1340.

#### **5. Safe Harbor and Stockpiling**

61. Under 35 U.S.C. § 271(e)(1), “[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented

invention...solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.”

62. However, the § 271(e)(1) exemption is not absolute, and “does not apply to information that may be routinely reported to the FDA, long after marketing approval has been obtained.” *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057, 1070-72 (Fed. Cir. 2011) (finding post-marketing clinical activities designed “to evaluate suggested associations between childhood vaccinations ... and risk of developing type 1 diabetes[,] and to determine whether timing of vaccination influences risk” insufficient to satisfy the § 271(e)(1) safe harbor). The Federal Circuit has also held that “routine quality control testing ... as part of the post-approval, commercial production process” is not reasonably related to the development and submission of information and fails to satisfy the requirements of the § 271(e)(1) safe harbor. *See Momenta Pharms., Inc. v. Teva Pharms. USA Inc.*, 809 F.3d 610, 620-21 (Fed. Cir. 2015).

63. The § 271(e)(1) exemption does not apply to all uses while FDA approval is pending. *Amgen Inc. v. Int’l Trade Comm’n*, 565 F.3d 846, 853 (Fed. Cir. 2009); *see also Biogen, Inc. v. Schering AG*, 954 F. Supp. 391, 396-97 (D. Mass. 1996) (“Biogen had done far more than merely do clinical trials for submission to the FDA, it had spent \$24 million to stockpile and prepare to market Avonex immediately upon the anticipated, imminent FDA approval in order to access promptly the lucrative market for beta interferon drugs to combat multiple sclerosis. These actions took Biogen out of the ‘safe harbor,’ made it subject to suit as of May 3, 1996, and gave it standing to sue itself.”).

64. In determining whether the safe harbor applies, “[e]ach of the accused activities must be evaluated separately.” *Amgen Inc. v. Hospira, Inc.*, 944 F.3d 1327, 1338 (Fed. Cir. 2019)

(quoting *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 200 (2005)).

65. The safe harbor does not apply to protect “non-FDA commercial manufacturing or yield optimization purposes.” *Wilson Wolf Mfg. Corp. v. Sarepta Therapeutics, Inc.*, No. CV 19-2316-RGA, 2020 WL 7771039, at \*5 (D. Del. Dec. 30, 2020); *see also Biogen*, 954 F. Supp. at 397 (finding the safe harbor does not apply where company “spent \$24 million to stockpile and prepare to market [drug] immediately upon the anticipated, imminent FDA approval in order to access promptly the lucrative market”); *Amgen, Inc. v. Hospira, Inc.*, 336 F. Supp. 3d 333, 344-45 (D. Del. 2018), *aff’d*, 944 F.3d 1327 (Fed. Cir. 2019).

66. “Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce, is surely not ‘reasonably related to the development and submission of information’ to the FDA.” *Merck*, 545 U.S. 193, 205-06.

## **6. Remedy**

67. If the product that the § 505(b)(2) applicant is likely to market would infringe a valid patent claim, then the patent owner is entitled to an order that FDA approval of the § 505(b)(2) Application containing the paragraph IV certification not be effective until the patent expires. 21 U.S.C. § 355(c)(3)(C)(ii).

68. If a Hatch-Waxman defendant’s application has already been approved by FDA, “the district court’s order would alter the effective date of the application, thereby converting a final approval into a tentative approval . . . . ‘In the case where an ANDA had been approved, the order would mandate a change in the effective date.’” *In re Omeprazole Pat. Litig.*, 536 F.3d 1361, 1367–68 (Fed. Cir. 2008) (quoting S.Rep. No. 98–547, at 46 (1984), as reprinted in 1984 U.S.C.C.A.N. 2647, 2679) (citing *Mylan Lab’ys, Inc. v. Thompson*, 389 F.3d 1272, 1281 (D.C. Cir.

2004)); *Vanda Pharms.*, 887 F.3d at 1138-39 (Fed. Cir. 2018) (“[U]pon a finding of patent infringement under § 271(e)(2), the district court must order remedies in accordance with § 271(e)(4).”); *see also Ortho-McNeil Pharm., Inc. v. Mylan Lab’ys Inc.*, No. CIV A 04-1689, 2007 WL 869545, at \*2 (D.N.J. Mar. 20, 2007) (“[T]he plain language here shows that Congress envisioned the factual scenario in which the ANDA had been approved, and intended that the district court then change the effective date.”) *aff’d in relevant part Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1366 (Fed. Cir. 2008) (“The district court was correct to reset the effective date of an ANDA directly under 35 U.S.C. § 271 without going through 21 U.S.C. § 355.”); *Eli Lilly & Co. v. Dr. Reddy’s Lab’ys, Ltd.*, No. 116CV00308TWMPMB, 2018 WL 3616715, at \*2 (S.D. Ind. July 27, 2018), *aff’d in relevant part sub nom. Eli Lilly & Co. v. Hospira, Inc.*, 933 F.3d 1320, 1324 (Fed. Cir. 2019) (“[T]he statutory language [of § 271(e)(4)(a)] including the word ‘shall’ requires that the Court reset the effective date of any approval, which is sufficient to resolve this case . . . . Although by the terms of the statute, injunctive relief is a discretionary remedy, resetting the effective date of approval is mandatory. The Federal Circuit has addressed this issue. . . . [R]esetting the effective date for approval is not a discretionary decision....” (citing *Vanda*, 887 F.3d at 1139)).

69. In Hatch-Waxman litigation, the right to a jury trial does not arise until there is a claim of infringement for which actual monetary damages can be recovered, e.g., if the defendant commercially launches their product “at-risk.” *See, e.g., Sepracor Inc. v. Dey L.P.*, No. CIV.A. 06-113-JJF, 2010 WL 2802611, at \*3 (D. Del. July 15, 2010); *Kao Corp. v. Unilever United States, Inc.*, Civ. No. 01–680, 2003 WL 1905635, \*3 (D. Del. Apr. 17, 2003).

70. Federal Rule of Civil Procedure 54(d)(1) states that “[u]nless a federal statute, these rules, or a court order provides otherwise, costs—other than attorney’s fees—should be allowed

to the prevailing party.”

**B. Contested Issues of Law**

**1. Infringement Under 35 U.S.C. § 271**

71. Whether Liquidia has infringed claims of the ’327 patent pursuant to 35 U.S.C. § 271(e) by submitting, maintaining, supplementing, amending, and/or resubmitting its § 505(b)(2) Application.

72. Whether Plaintiff has proven by a preponderance of the evidence that Defendant would infringe Asserted Claims 1-11 and 14-19 of the ’327 patent pursuant to 35 U.S.C. § 271(a) by making, selling, or offering to sell Defendant’s Proposed Product.

73. Whether Plaintiff has proven by a preponderance of the evidence that Defendant would induce physicians, caregivers, and patients to infringe Asserted Claims 1-11 and 14-19 of the ’327 patent pursuant to 35 U.S.C. § 271(b) by encouraging physicians, caregivers, and patients to administer Defendant’s Proposed Product according to Defendant’s proposed label and proposed instructions for use.

74. Whether Plaintiff has proven by a preponderance of the evidence that Defendant has an affirmative intent to induce direct infringement of one or more of Asserted Claims 1-11 and 14-19 of the ’327 patent.

75. Whether Defendant’s conduct of its ongoing ASCENT clinical trial meets the requirements of the 35 U.S.C. § 271(e)(1) safe harbor.

76. Whether Plaintiff has proven by a preponderance of the evidence that Defendant’s conduct of its ongoing ASCENT clinical trial has infringed one or more of Asserted Claims 1-11 and 14-19 of the ’327 patent under 35 U.S.C. § 271(a) and/or 35 U.S.C. § 271(b).

77. Whether Plaintiff has proven by a preponderance of the evidence that Defendant

willfully infringed one or more of Asserted Claims 1-11 and 14-19 of the '327 patent.

## **2. Remedy**

78. Whether judgment should be entered pursuant to 35 U.S.C. § 271(e)(2)(A) finding Liquidia committed an act of infringement by submitting a 505(b)(2) Application “for a drug claimed in a patent or the use of which is claimed in a patent.”

79. Whether judgment should be entered pursuant to 35 U.S.C. § 271(e)(4), providing the following remedies for an act of infringement described in § 271(e)(2)(A):

80. providing that the effective date of any FDA approval for Liquidia commercially to make, use, or sell the drug products that are the subjects of Liquidia’s § 505(b)(2) Application be not earlier than the expiration date of the '327 patent; and

81. enjoining Liquidia from commercially manufacturing, using, offering to sell, or selling within the United States, or importing into the United States, the drug products that are the subject of Liquidia’s § 505(b)(2) Application.

82. Whether judgment should be entered pursuant to 35 U.S.C. § 271(a) enjoining Liquidia from making, using, marketing, offering to sell, or selling the drug product that is the subject of Liquidia’s § 505(b)(2) Application, or importing into the United States the drug product that is the subject of Liquidia’s § 505(b)(2) Application, during the term of the '327 patent.

83. Whether judgment should be entered pursuant to 35 U.S.C. § 271(b) enjoining Liquidia from making, using, marketing, offering to sell, or selling the drug product that is the subject of Liquidia’s § 505(b)(2) Application, or importing into the United States the drug product that is the subject of Liquidia’s § 505(b)(2) Application, during the term of the '327 patent.

84. Whether judgment should be entered finding that Liquidia’s infringement of the '327 patent has been willful.



85. Whether UTC should be awarded costs.

86. Whether judgment should be entered pursuant to 35 U.S.C. §§ 271(a)-(b),(e) against Liquidia on Liquidia's counterclaims seeking declaratory relief of non-infringement of '327 patent.

#### **IV. VALIDITY**

##### **A. Legal Standards**

##### **1. Presumption of Validity**

87. Issued patent claims are presumed by statute to be valid. 35 U.S.C. § 282.

88. It is Liquidia's burden to overcome the presumption of validity with clear and convincing evidence of invalidity. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242, 2244 (2011). Patent challengers have the heavy burden of proving invalidity by clear and convincing evidence, and that burden of persuasion never shifts to the patentee. *Id.* at 2242, 2244, 2245-46, 2248; *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1077-78 (Fed. Cir. 2012); *Data Health Partners, Inc. v. Teladoc Health, Inc.*, 734 F. Supp. 3d 315, 327 (D. Del. 2024) ("Deference to a patent examiner's decision to allow claims is incorporated into the presumption of patent validity under 35 U.S.C. § 282.")

89. Evidence that gives rise to an "abiding conviction that the truth of [the] factual contentions are 'highly probable'" is considered clear and convincing evidence. *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984). The presumption of validity, and the burden of proof in overcoming that presumption, applies to each claim of the patent independently. *See* 35 U.S.C. § 282(a); *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1581 n.8 (Fed. Cir. 1993). A patent may be found valid "solely on the failure of the patent challenger's evidence to convincingly establish the contrary." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d

1565, 1570 (Fed. Cir. 1986) (emphasis in original); see also *Jones v. Hardy*, 727 F.2d 1524, 1529 & n.3 (Fed. Cir. 1984).

90. “[A] party challenging validity shoulders an enhanced burden if the invalidity argument relies on the same prior art considered during examination by the [U.S. Patent Office].” *Creative Compounds, LLC v. Starmark Lab’ys.*, 651 F.3d 1303, 1313 (Fed. Cir. 2011) (quoting *Tokai Corp. v. Easton Enterprs., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011)); *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004) (noting that the burden of showing invalidity to be “especially difficult” when the infringer relies on prior art presented to the patent examiner during prosecution). *Impax Lab’ys., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008) (“When the examiner considered the asserted prior art and basis for the validity challenge during patent prosecution, [the clear and convincing evidence] burden becomes particularly heavy.”); see also *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 704–05 (Fed. Cir. 2012).

## **2. Priority**

91. A patentee is entitled to a priority date that is earlier than the filing date of the patent application when, inter alia, a previous application disclosed the invention in compliance with § 112. *See* 35 U.S.C. § 120 (“An application for patent for an invention disclosed in the manner provided by section 112(a) . . . in an application previously filed in the United States . . . shall have the same effect, as to such invention, as though filed on the date of the prior application . . .”).

92. The AIA does not change the burden-of-proof when the patentee seeks to claim an earlier priority date to avoid prior art. *See B-5, Inc. v. Accu-Tac, LLC*, No. EDCV 20-532, 2022 WL 1584499, at \*1, \*5 (C.D. Cal. Mar. 1, 2022) (finding patentee “b[ore] the burden of proving that the [patent was] entitled to a priority date before the filing date of the [patent] application,”

which was filed on March 26, 2013); *Jackson v. NuVasive, Inc.*, No. CA 21-53-RGA, 2023 WL 5175092, at \*6 (D. Del. Aug. 11, 2023) (concluding “[t]he patentee bears the burden of establishing that the claimed invention is entitled to an earlier priority date than an asserted prior art reference” in a case where patents at issue were filed between 2015 and 2020), *adopted by* 2023 WL 6387866 (D. Del. Sept. 29, 2023), ECF No. 148 (Andrews, J.).

93. In the circumstance where a challenger asserts prior art that was published before the filing date of a nonprovisional patent application, the patentee bears the burden of production—or “going forward with” evidence—that it is entitled to the earlier priority date. *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008); *see Orexigen Therapeutics, Inc. v. Actavis Lab’ys. FL, Inc.*, 282 F. Supp. 3d 793, 805 (D. Del. 2017) (Andrews, J.) (noting in dicta that “the burden of establishing entitlement to the priority date of a provisional application rests with the party claiming priority”), *aff’d in part, rev’d in part on other grounds sub nom. Nalpropion Pharms., Inc. v. Actavis Lab’ys FL, Inc.*, 934 F.3d 1344 (Fed. Cir. 2019).

94. Having the burden of production means “going forward with evidence,” which the Federal Circuit defines as “producing additional evidence and presenting persuasive argument based on new evidence or evidence already of record, as the case may require.” *Tech. Licensing*, 545 F.3d at 1327; *see also Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 958, 966 (Fed. Cir. 2023) (finding that the patentee had met its burden of production to show that the patent-in-suit was entitled to its earliest priority date).

95. A statement in the prosecution history that amounts to a USPTO determination that the claims of the patent find support in the provisional application would satisfy the patentee’s burden of production. *See PowerOasis, Inc., v. T-Mobile USA, Inc.*, 5252 F.3d 1299, at 1304-05 (Fed. Cir. 2008); *Janssen Pharms., Inc. v. Tolmar, Inc.*, 718 F. Supp. 3d 394, 414-15 (D. Del.

2024).

96. “Once [the patentee] meets [its] burden of production, the burden shifts back to Defendants to prove by clear and convincing evidence that [the patentee is] not entitled to the earlier date.” *Endo Pharms. Inc. v. Actavis Inc.*, No. 14-1381, 2017 WL 3731001, at \*4 (D. Del. Aug. 30, 2017) (Andrews, J.).

97. The ultimate burden of persuasion—and the “risk of decisional uncertainty”—remains with the patent challenger as to whether the patent is invalid as obvious or anticipated. *See Tech. Licensing*, 545 F.3d at 1327.

### **3. What Constitutes Prior Art**

98. “Under the AIA, whether a reference is prior art is determined based on ‘the effective filing date of the claimed invention,’ rather than the date of the invention.” *Sanho Corp. v. Kaijet Tech. Int’l Ltd.*, 108 F.4th 1376, 1380 (Fed. Cir. 2024) (quoting 35 U.S.C. § 102(a)).

99. To establish that a reference qualifies as prior art due to its public accessibility, e.g., under 35 U.S.C. § 102(a)(1), it is the patent challenger’s burden to present sufficient evidence to establish that the reference was publicly accessible before the priority date of the patent. *MHL Custom, Inc. v. Waydoo USA, Inc.*, No. CV 21-0091-RGA, 2023 WL 5748755, at \*3 (D. Del. Sept. 6, 2023) (defendant “did not meet its heavy evidentiary burden to show [reference] was publicly accessible.” (applying post-AIA law)); *see also Kyocera Wireless Corp. v. Int’l Trade Comm’n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008). “[P]rior art includes other patent applications effectively filed, or other patents issued, before the effective filing date of the patent at issue. *Sanho Corp.*, 108 F.4th at 1380 (quoting 35 U.S.C. § 102(a)(1)). “Section 102(a)(1) also defines prior art to include situations in which the claimed invention was ‘described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the

claimed invention.” *Id.* “However, Congress provided exceptions for certain references that would otherwise be prior art. These exceptions fit into two broad categories.” *Id.*

100. “First, section 102(b) contains two largely parallel exceptions at subsections (b)(1)(A) and (b)(2)(A). *Id.* The subsection (b)(1)(A) exception applies to disclosures covered by section 102(a)(1) (‘described in a printed publication, or in public use, on sale, or otherwise available to the public’) created within one year before patent filing. *Id.* (quoting 35 U.S.C. § 102(b)(1)). It provides a prior art exception for a ‘disclosure’ that was either ‘made by the inventor . . . or by another who obtained the subject matter disclosed directly or indirectly from the inventor.’” *Id.* (quoting 35 U.S.C. § 102(b)(1)).

101. “The parallel provision at subsection (b)(2)(A) applies to disclosures covered by section 102(a)(2) (patent applications filed by another). *Id.* It provides a prior art exception for ‘subject matter disclosed’ that ‘was obtained directly or indirectly from the inventor.’ *Id.* (quoting 35 U.S.C. § 102(b)(1)). Subsection (b)(2)(A) is not limited to disclosures in the one-year grace period. *Id.* at 1381. Together, subsections (b)(1)(A) and (b)(2)(A) operate in the context of the first-inventor-to-file regime to provide protection for otherwise invalidating disclosures by the patentee or by someone who obtained the subject matter from the patentee, whether directly or indirectly. *Id.* These subsections do not include a ‘publicly disclosed’ requirement.” *Id.*

102. “What evidence is necessary to show that the disclosure is an inventor-originated disclosure requires case-by-case treatment, depending upon whether it is apparent from the disclosure itself or the patent application specification that the disclosure is an inventor-originated disclosure.” MPEP § 2153.01(a).

103. Further, according to MPEP § 2155.03,

An applicant may also show that another obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor

in an affidavit or declaration under 37 CFR 1.130(b). Thus, an applicant may establish a prior public disclosure by another during the grace period if the applicant can establish [1] that subject matter disclosed originated with the inventor or a joint inventor and [2] that the subject matter was communicated by the inventor or a joint inventor, directly or indirectly. Any documentation which provides evidence of the communication of the subject matter by the inventor or a joint inventor to the entity that made the disclosure of the subject matter directly or indirectly, such as by an assignee of the inventor, should accompany the affidavit or declaration.

104. The burden of determining whether a prior art reference qualifies as a disclosure by an inventor mirrors the allocation in the context of claiming an earlier priority date. *See Cellulose Material Sols., LLC v. SC Mktg. Grp., Inc.*, 719 F. Supp. 3d 1052, 1058-59 (N.D. Cal. 2024) (citing *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008)).

105. “Section 102(b) contains two provisions directed at disclosures by another (that is, not by the inventor) after the ‘subject matter disclosed’ was ‘publicly disclosed by the inventor’ in subsections (b)(1)(B) and (b)(2)(B). *Sanho Corp.*, 108 F.4th at 1381. Subsection (b)(1)(B) refers to activities by the inventor or a third party that would otherwise be invalidating disclosures under section 102(a)(1) (‘described in a printed publication, or in public use, on sale, or otherwise available to the public’) made within one year of the patent filing, and subsection (b)(2)(B) refers to patent applications by another (section 102(a)(2) disclosures) that disclosed the ‘subject matter [already] disclosed’ by the inventor, without regard to the one-year time limit. In summary, these provisions except from prior art disclosures that were made after the invention was ‘publicly disclosed’ by the inventor.” *Id.* at 1381 (quoting 35 U.S.C. § 102(b)).

106. “A disclosure” shall not be prior art to a claimed invention . . . if . . . the subject matter disclosed and the claimed invention, not later than the effective filing date of the claimed invention, were owned by the same person or subject to an obligation of assignment to the same person.” 35 U.S.C. § 102(b)(2)(C).

107. Whether a document is a “printed publication” that qualifies as prior art is determined by the “public accessibility” of the document. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348 (Fed. Cir. 2016). The public accessibility of a document is the “touchstone in determining whether a reference constitutes a printed publication.” *Kyocera*, 545 F.3d at 1350 (internal citations omitted). A document is publicly accessible if it was “disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it.” *Id.*

108. To determine whether a reference is publicly available, several factors must be considered:

- (1) distribution or dissemination; (2) records accessible to the public; (3) indexing and cataloging in a meaningful way; (4) duration of the display; (5) expertise of the intended audience; (6) expectations regarding the copying of the information displayed; and (7) ease or simplicity with which a display could be copied.

*Energy Transp. Grp. v. William Demant Holding A/S*, C.A. No. 05-422 GMS, 2008 WL 11335094, at \*1 (D. Del. Jan. 18, 2008) (citations omitted) (citing *In re Klopfenstein*, 380 F.3d 1345, 1350–51 (Fed. Cir. 2004); *In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989); *In re Hall*, 781 F.2d 897 898–99 (Fed. Cir. 1986); *In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981)).

#### **4. Anticipation Under 35 U.S.C. § 102**

##### **a) Generally**

109. “[A]nticipation is a question of fact that must be established at trial by clear and convincing evidence.” *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (citation omitted). “A determination that a patent is invalid as being anticipated under 35 U.S.C. § 102 requires a finding that ‘each and every limitation is found either expressly or inherently in a single prior art reference.’” *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1375 (Fed. Cir. 2006); *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014). Limitations that are

missing from a prior art reference cannot be filled in simply because a skilled artisan would be able to envision them. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274-75 (Fed. Cir. 2017) (“*Kennametal* does not permit the Board to fill in missing limitations simply because a skilled artisan would immediately envision them.” (distinguishing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381-83 (Fed. Cir. 2015))).

110. “In order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation.” *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312, 1314 (Fed Cir. 2008). The anticipating reference must enable all the “subject matter that falls within the scope of the claims at issue.” *Galderma Labs., L.P. v. Teva Pharms. USA, Inc.*, 799 F. App’x 838, 842-843 (Fed. Cir. 2020) (quoting *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009)). Factors to be considered in determining whether a disclosure would require undue experimentation include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). “[F]ailures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.” *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013) (“This court has held that experimentation was unreasonable, for example, where it was found that eighteen months to two years’ work was required to practice the patented invention.”) (citing *White Consol. Indus., Inc. v. Vega Servo-Control, Inc.*, 713 F.2d 788, 791 (Fed. Cir. 1983)). Experimentation may also be undue where the reference “lacks guidance by teaching away from the subject matter that was



eventually claimed.” *Id.*; *see also White*, 713 F.2d at 791 (“testif[ying] in this case that development of a single pass language translator would require from 1 ½ to 2 man years of effort, a clearly unreasonable requirement”).

111. To the extent that a POSA’s “knowledge of the art” is relevant to the enablement inquiry, the relevant knowledge is “what would have been understood by one of ordinary skill in the art at the time of [the prior art’s] publication”—not the patent’s priority date. *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1356 (Fed. Cir. 2005).

**b) Inherent Anticipation**

112. “To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently.” *Rapoport v. Dement*, 254 F.3d 1053, 1057 (Fed. Cir. 2001). “Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claims limitations, it anticipates.” *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005). Inherency “may not be established by probabilities or possibilities”—“[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.” *Rapoport*, 254 F.3d at 1063. For instance, a Phase I study describing the use of a drug compound does not inherently anticipate when the form of the drug (crystalline or amorphous) is not specified and any of the possible forms could potentially be used. *Pharmacyclic LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 413–14 (D. Del. 2021).

113. A new use of a known process is patentable. *Perricone*, 432 F.3d at 1378; *Rapoport*, 254 F.3d at 1063. The *Perricone* court held that a claimed method for treating sunburn by topically applying a compound to a sunburn was a new use that was not inherently anticipated by a prior art method of using the same composition for general topical application. *Perricone*, 432 F.3d at 1379. The Federal Circuit reasoned that the prior art was “silent about any sunburn prevention or treatment benefits, not to mention the mechanisms underlying such uses.” *Id.* The court further

noted that “sunburn is not analogous to skin surfaces generally,” so “there is an important distinction between topical application to skin for the purpose of avoiding sunburn, and the much narrower topical application to skin sunburn.” *Id.* Likewise, the court in *Rapoport* concluded that a claimed method for administering a drug to treat sleep apnea was a new use that was not inherently anticipated by a prior art method of using the same drug to treat anxiety—a symptom of sleep apnea. *Rapoport*, 254 F.3d at 1061-63. The court there emphasized that the prior art did not disclose tests in which the drug was administered to patients suffering from sleep apnea with the intent to cure the underlying condition. *Id.* at 1061-62.

114. “It is of no matter if the missing limitation often or usually would result from practice of the earlier claim—there is no inherent anticipation unless the missing limitation is present each and every time the earlier claim is practiced.” *In re Afibercept Pat. Litig., aff’d sub nom. Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, No. 2024-2009, 2025 WL 324288 (Fed. Cir. Jan. 29, 2025); *see also Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, No. CV 20-430-RGA, No. CV 20-430-RGA, 2022 WL 3225381, at \*7 (D. Del. Aug. 10, 2022), *aff’d*, 98 F.4th 1056 (Fed. Cir. 2024), and *aff’d*, 98 F.4th 1056 (Fed. Cir. 2024) (“While Viscomi 2008’s increased specificity in the method of preparation suffices to suggest that Cannata may not produce rifaximin  $\beta$  each and every time (as would be required for inherent anticipation), the standard for obviousness is a reasonable expectation of success.”); *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 343 F. Supp. 3d 823, 846 (N.D. Ill. 2018), *aff’d*, 946 F.3d 1322 (Fed. Cir. 2020) (similar).

115. Thus, in order for a prior art method of treating one condition to inherently anticipate a claimed method of treating a second condition with the same drug, the prior art method must necessarily treat patients as claimed. *Glaxo Grp. Ltd. v. Kali Lab’ys, Inc.*, No. CIVA03-CV-399 (JLL), 2005 WL 1398507, at \*4 (D.N.J. June 10, 2005) (the prior art method must, as “a

necessary consequence of what was deliberately intended,” yield the result taught by the claimed method). This requirement is only met if “virtually all the designated recipients of the drug under [the prior art method] ... also suffer[] from [the claimed condition or symptom], in which case the administration of [the drug] demonstrated by [the prior art method] would necessarily result in the outcome claimed.” *Id.* at \*4.

116. “[I]t is well settled that a narrow species can be . . . patent eligible despite a patent on its genus.” *Prometheus Lab’ys, Inc. v. Roxane Lab’ys, Inc.*, 805 F.3d 1092, 1098 (Fed. Cir. 2015); *Metabolite Lab’ys, Inc. v. Lab’y Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (“A prior art reference that discloses a genus still does not inherently disclose all species within that broad category.”).

117. While *Prometheus* discussed this genus-species distinction in the context of obviousness, the District of Delaware has applied this logic to inherency as well. *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 591-92 (D. Del. 2018) (“Although [*Prometheus*] addressed the question in the context of obviousness, there is no reason why that approach is not equally applicable to the issue of inherency in the setting in which the asserted claims recite treating a subset of patients, and a prior art reference recites treating patients generally.”), *aff’d sub nom. Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019). *Prometheus* explains that this “genus-species distinction may have particular relevance in the field of personalized medicine, where, for example, a particular treatment may be effective with respect to one subset of patients and ineffective (and even harmful) to another subset of patients.” *Prometheus*, 805 F.3d at 1098. In such a case, “[s]ingling out a particular subset of patients for treatment ... may reflect a new and useful invention that is patent eligible despite the existence of prior art or a prior art patent disclosing the treatment method to

patients generally.” *Id.* *Prometheus* further explains that a “rejection likely would not be appropriate where the new patient subset displayed unexpected results.” *Id.*

118. As *Pernix* further explains, the genus-species approach of showing inherent anticipation “turns on whether the genus was of such a defined and limited class that one of ordinary skill in the art could ‘at once envisage’ each member of the genus.” *Id.* at 591. To find anticipation, “the generic reference must identify the claimed species with ‘sufficient specificity’; that is, the reference must express ‘specific preferences’ for one or more particular species or must disclose a genus that is sufficiently small that the disclosure of the genus effectively describes the species.” *Id.* “The standard for finding that a prior art genus anticipates an incorporated species is significantly more restrictive than the standard for determining whether a prior art genus renders obvious a species that is incorporated within it.” *Id.*

### **c) Prior Public Use**

119. “Public use includes ‘any use of [the claimed] invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor.’” *Netscape Commc'ns Corp. v. Konrad*, 295 F.3d 1315, 1320 (Fed. Cir. 2002) (alteration in original); *Minerva Surgical, Inc. v. Hologic, Inc.*, 59 F.4th 1371, 1377 (Fed. Cir. 2023) (“The ‘in public use’ element of the bar is met if the invention ‘was accessible to the public or was commercially exploited’ by the inventor. ‘An invention is in public use if it is shown to or used by an individual other than the inventor under no limitation, restriction, or obligation of confidentiality.’”) (internal citations omitted).

120. As with the on-sale bar, the invention must also be ready for patenting. *Minerva Surgical, Inc. v. Hologic, Inc.*, 59 F.4th 1371, 1377 (Fed. Cir. 2023).

121. Courts look to the totality of the circumstances when evaluating whether there has been a public use. *Netscape Commc'ns Corp. v. Konrad*, 295 F.3d 1315, 1320 (Fed. Cir. 2002).

“These circumstances may include:” (1) “the nature of the activity that occurred in public;” (2) “the public access to and knowledge of the public use;” (3) “whether there was any confidentiality obligation imposed on persons who observed the use;” and (4) if the use is related to testing: (a) “whether persons other than the inventor performed the testing;” (b) “the number of tests;” (c) “the length of the test period in relation to tests of similar devices;” and (d) “whether the inventor received payment for the testing.” *Id.*

122. A clinical study may not anticipate if the study was “kept sufficiently confidential to avoid a finding of ‘public use.’” *Dey, L.P. v. Sunovion Pharms., Inc.*, 715 F.3d 1351, 1357 (Fed. Cir. 2013) (“Investigators were the most knowledgeable persons involved in the study, and they were required to sign a pledge of confidentiality,” but while the patients “were informed about the active chemical compound and the range of possible dosages being investigated, they were not even told the identity of the particular drug or formulation they were receiving. Therefore, “while it is true that participants were permitted to discuss the study with their doctors, they were not in a position to reveal the composition of the allegedly invalidating prior art, because they were unaware of the specifics of the inventive formulations.”).

123. A public use does not trigger the public-use bar if the inventor is engaged, in good faith, in testing the operation of his invention. *City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 127 (1877).

**d) Prior Sale**

124. The on-sale bar applies when two conditions are satisfied before the critical date: (1) the product embodying the claimed invention was the subject of a commercial offer for sale; and (2) the claimed invention was ready for patenting. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67 (1998); *Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 586 U.S. 123, 125-26 (2019) (holding that the AIA did not alter the meaning of “on sale” or the standard set forth in *Pfaff*).

125. The “ready for patenting” condition must be satisfied by “proof of reduction to practice before the critical date, or by proof that prior to the critical date the inventor had prepared drawings or other descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention.” *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67-68 (1998). The Supreme Court rejected formulations that would require only that the invention be “substantially complete” or reduced to practice at the time the offer for sale was made. *Id.* at 66 (“The word ‘invention’ must refer to a concept that is complete, rather than merely one that is ‘substantially complete.’”).

126. Subsequent completion of an invention after the critical date will not relate back to validate an earlier offer for sale. *Robotic Vision Sys., Inc. v. View Eng’g, Inc.*, 112 F.3d 1163, 1167–68 (Fed. Cir. 1997) (“[T]he later completion of an invention concerning which an alleged offer to sell had been made earlier does not relate back to the date of that offer.”); *see also Sparton Corp. v. United States*, 399 F.3d 1321, 1324–25 (Fed. Cir. 2005) (noting that an offer for sale made before the inventor completed its conception of the invention should not create an on-sale bar, as what was offered could not be the “invention”).

127. To trigger the on-sale bar, “[t]he invention itself must be sold or offered for sale, and the mere existence of a ‘commercial benefit . . . is not enough’ . . . on its own.” *BASF Corp. v. SNF Holding Co.*, 955 F.3d 958, 969 (Fed. Cir. 2020) (citing *Medicines Co. v. Hospira, Inc.*, 827 F.3d 1363, 1373 (Fed. Cir. 2016) (en banc)).

128. To successfully invalidate a patent claim based on the on-sale bar, clear and convincing evidence is required. *Gemmy Indus. Corp. v. Chrisha Creations Ltd.*, 452 F.3d 1353, 1358 (Fed. Cir. 2006).

129. “Offer for sale” or “sale” under § 271(a) is defined according to traditional

contractual norms. *Rotec Indus., Inc. v. Mitsubishi Corp.*, 215 F.3d 1246, 1254-55 (Fed. Cir. 2000). A “sale” is a contract between parties to transfer property rights for consideration, where the buyer pays or promises to pay the seller. *In re Caveney*, 761 F.2d 671, 676 (Fed. Cir. 1985); *see also Grp. One, Ltd. v. Hallmark Cards, Inc.*, 254 F.3d 1041, 1047 (Fed. Cir. 2001) (noting that courts “will look to the Uniform Commercial Code . . . to define whether . . . a communication or series of communications rises to the level of a commercial offer for sale.”). “To meet the first, commercial offer, prong, the offer must be sufficiently definite that another party could make a binding contract by simple acceptance, assuming consideration. In determining such definiteness, we review the language of the proposal in accordance with the principles of general contract law.” *Atlanta Attachment Co. v. Leggett & Platt, Inc.*, 516 F.3d 1361, 1365 (Fed. Cir. 2008) (internal citations omitted).

130. For an on-sale bar to apply, the product or process sold or offered for sale must embody every limitation of the claimed invention, such that, the first step in this analysis is to determine if the subject of the sale met each claim limitation and thus embodied the invention. *Scaltech Inc. v. Retec/Tetra, L.L.C.*, 178 F.3d 1378, 1383 (Fed. Cir. 1999).

131. To trigger the on-sale bar under § 102(b), a sale or offer for sale must involve an offer to actually perform the claimed process because an offer that merely exchanges details about how to perform a claimed process, without an actual offer to carry out the process itself, does not suffice. *In re Kollar*, 286 F.3d 1326, 1332–33 (Fed. Cir. 2002). The exchange of details of how to perform a claimed process without an offer of actual performance does not suffice to invoke the on-sale bar. *Id.* at 1332.

#### **e) Experimental Use Exception**

132. “The proper test for the public use prong . . . is whether the purported use: (1) was accessible to the public; or (2) was commercially exploited.” *Invitrogen Corp. v. Biocrest Mfg.*,

*L.P.*, 424 F.3d 1374, 1380 (Fed. Cir. 2005). “[A]n inventor who seeks to perfect his discovery may conduct extensive testing without losing his right to obtain a patent for his invention—even if such testing occurs in the public eye.” *Pfaff v. Wells Elecs.*, 525 U.S. 55, 64 (1998);

133. Whether a public use qualifies as an experimental use is a question of law and is determined by the totality of the circumstances. *See, e.g., Petrolite Corp. v. Baker Hughes Inc.*, 96 F.3d 1423, 1426 (Fed. Cir. 1996). If public use is established by clear and convincing evidence, *ART+COM Innovationpool GmbH v. Google, Inc.*, 155 F. Supp. 3d 489, 501 (D. Del. 2016), the burden shifts to the inventor to prove “with convincing evidence that the public use activities fall within the experimental use exception,” *In re Smith*, 714 F.2d 1127, 1135 (Fed. Cir. 1983).

134. “A use may be experimental if its purpose is: ‘(1) [to] test claimed features of the invention or (2) to determine whether an invention will work for its intended purpose.’” *Polara Eng’g Inc v. Campbell Co.*, 894 F.3d 1339, 1348 (Fed. Cir. 2018) (alteration in original). In determining whether a use is experimental, courts consider the following factors: “(1) the necessity for public testing, (2) the amount of control over the experiment retained by the inventor, (3) the nature of the invention, (4) the length of the test period, (5) whether payment was made, (6) whether there was a secrecy obligation, (7) whether records of the experiment were kept, (8) who conducted the experiment, (9) the degree of commercial exploitation during testing, (10) whether the invention reasonably requires evaluation under actual conditions of use, (11) whether testing was systematically performed, (12) whether the inventor continually monitored the invention during testing, and (13) the nature of contacts made with potential customers.” *Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1328 (Fed. Cir. 2019).

135. “[E]vidence of experimental use may negate either the ‘ready for patenting’ or ‘public use’ prong.” *Invitrogen*, 424 F.3d at 1379–80.



136. A public use may occur when “a completed invention is used in public, without restriction.” *Allied Colloids Inc. v. Am. Cyanamid Co.*, 64 F.3d 1570, 1574 (Fed. Cir. 1995); *see W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1549 (Fed. Cir. 1983) (“The nonsecret use of a claimed process in the usual course of producing articles for commercial purposes is a public use.”). “[A] disclosure of some aspects of an invention, but not all, will likely preclude a finding of public use.” *Pronovo Biopharma Norge AS v. Teva Pharm. USA, Inc.*, 549 F. App’x 934, 939 (Fed. Cir. 2013).

137. The experimental use doctrine negates the public use bar under post-AIA § 102, as it did under pre-AIA law. *See Dzinesquare, Inc. v. Armano Luxury Alloys, Inc.*, No. CV 14-01918 JVS, 2014 WL 12597154, at \*4 n.5 (C.D. Cal. Dec. 22, 2014) (citing *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 67–68 (1998)) (finding that the on-sale bar, public use, and printed publication bars should be interpreted the same under post-AIA § 102 as it was under pre-AIA § 102). In general, “[a] use may be experimental if its purpose is: ‘(1) [to] test claimed features of the invention or (2) to determine whether an invention will work for its intended purpose . . . .’” *Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1328 (Fed. Cir. 2019) (alteration in original).

138. “The experimental-use inquiry asks whether the inventor’s conduct would lead the “‘public” to reasonably believe the invention was in the public domain,’ and in particular whether there has been ‘any use of that invention by a person *other than the inventor* who is under no limitation, restriction or obligation of secrecy to the inventor.’” *Id.* at 1330 (internal citations omitted) (emphasis added); *see also In re Hamilton*, 882 F.2d 1576, 1581 (Fed. Cir. 1989) (“The experimental use doctrine operates in the inventor’s favor to allow *the inventor* to refine his invention or to assess its value relative to the time and expense of prosecuting a patent application. If it is not the inventor or someone under his control or ‘surveillance’ who does these things, there

appears to us no reason why he should be entitled to rely upon them to avoid the statute.”) (emphasis in original).

139. Under the experimental use doctrine, “[p]roof of experimental use serves as ‘a negation of the statutory bars’ of § 102(b). *Polara Eng’g*, 894 F.3d at 1348 (quoting *EZ Dock v. Schafer Sys., Inc.*, 276 F.3d 1347, 1352 (Fed. Cir. 2002)); see also, e.g., *Eli Lilly v. Zenith*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) (“The trial court concluded that Lilly’s clinical trials of olanzapine were not a public, but an experimental, use that negated any section 102 bar.”) Thus, proof of experimental use means that use of an invention and associated disclosures are not prior art to a patent on that invention. See, e.g., *In re Cecarelli*, 401 F. App’x 553, 554 (Fed. Cir. 2010) (“Because the sale was for experimental use, the product sold is not prior art. (citing *Dippin’ Dots, Inc. v. Mosey*, 476 F.3d 1337, 1344 (Fed. Cir. 2007) (internal citation omitted)).

140. Courts have considered 13 factors for determining whether a use is experimental, which are set out in *Polara Eng’g*, 894 F.3d 1339, 1348-49 (Fed. Cir. 2018). See also *Clock Spring, L.P. v. Wrapmaster, Inc.*, 560 F.3d 1317, 1327 (Fed. Cir. 2009) (quoting *Allen Eng’g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1353 (Fed. Cir. 2002)).

141. Experimentation with a non-claimed utility of the claimed invention may constitute experimental use, even where not *explicitly* recited in the claims. See *EZ Dock*, 276 F.3d at 1353–54 (finding experimental use when an invention claiming “a floating dock” was tested in choppy water because “floating docks, by their nature, must endure all kinds of water conditions”); *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 551 (Fed. Cir. 1990) (“When durability in an outdoor environment is inherent to the purpose of an invention, then further testing to determine the invention’s ability to serve that purpose will not subject the invention to a section 102(b) bar.”— (referring to U.S. Patent No. 3,847,333 (filed Feb. 1, 1973), where durability was

not claimed);.

142. “Several indicia may show the negating experimental character of a use, including (1) the length of the test period, (2) any confidentiality agreement, (3) any records of testing, (4) any monitoring and control of the test results, (5) the number of tests, and (6) the length of the test period in relation to tests of similar inventions.” *Eli Lilly & Co.*, 471 F.3d at 1381 (finding no public use because Lilly “tailored its tests to their experimental drug safety and efficacy purpose, adequately monitored for results, and maintained confidentiality throughout the duration of the study”).

143. A pharmaceutical composition undergoing clinical trials to determine whether the invention will work for its intended purpose has not been reduced to practice. *See Sanofi*, 204 F. Supp. 3d at 698. The fact that a clinical trial is required may support that a drug has not yet been reduced to practice. *See id.* (“The fact that dronedarone’s clinical benefit was uncertain before the critical date is further highlighted by the fact that the FDA and EMEA essentially required that Sanofi hold the ATHENA trial to show that dronedarone could provide a clinical benefit to patients with AF and associated risk factors in a safe and effective manner.”). The experimental use doctrine protects inventions that have not yet been reduced to practice. *See In re Omeprazole Pat. Litig.*, 536 F.3d 1361, 1372 (Fed. Cir. 2008); *see also Allen Eng’g Corp.*, 299 F.3d at 1354 *see also In re Omeprazole Pat. Litig.*, 536 F.3d at 1373–74 (demonstrating patentee’s clinical trials were required to confirm effectiveness and therefore, the invention had not been reduced to practice before the clinical studies were complete).

144. Clinical trials to determine the efficacy of a drug constitute experimental use within the meaning of the experimental use doctrine. *See, e.g., Sanofi v. Glenmark Pharms. Inc., USA*, 204 F. Supp. 3d 665, 698 (D. Del. 2016) (“[A] clinical trial seeking to test a particular treatment

hypothesis seems to be the quintessential experimental use.”); *Gilead Scis. v. Sigmapharm Labs*, No. CIV.A. 10-4931 (SDW)(MCA), 2014 WL 1293309, at \*6 (DNJ March 31, 2014) (stating that “[c]linical trials conducted to determine the efficacy of a drug candidate have been found to be an example of experimental use negation of the statutory bar” (citing *Bayer Schering Pharma AG v. Barr Labs., Inc.*, No. 05-cv-2308, 2008 WL 628592 (D.N.J. Mar.3, 2008))); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380–81 (Fed. Cir. 2006) (finding that the “experimental character” of the clinical trials negated the public use bar); *Boston Sci. Corp., v. Cordis Corp.*, No. C 02-01474 JW, 2008 WL 11387141, at \*7 (N.D. Cal. Jan, 25, 2008) (finding clinical trials were experimental because the purpose “was to establish . . . that the GDC system was safe and effective when ‘used to occlude aneurysm and arteriovenous malformations,’” and an element of the claimed invention was “occluding a cavity in humans”).

145. Experimentation undertaken to satisfy a regulatory requirement is not *per se* experimental but can be experimental for the purpose of negating the statutory bar “if it represents a bona fide effort to perfect the invention or to ascertain whether it will answer its intended purpose.” *Pennwalt Corp. v. Akzona, Inc.*, 740 F.2d 1573, 1580 (Fed. Cir. 1984).

## **5. Obviousness Under 35 U.S.C. § 103**

### **a) Generally**

146. The ultimate determination of obviousness is a question of law based on underlying factual findings, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) such secondary considerations as commercial success, long-felt but unmet need, failure of others, etc. See *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Endo Pharms., Inc. v. Actavis LLC*, 922 F.3d 1365, 1372–373 (Fed. Cir. 2019).

147. The defendant has the burden of proof with respect to all of the *Graham* factors. *Am. Hosp. Supply Corp. v. Travenol Labs., Inc.*, 745 F.2d 1, 8 (Fed. Cir. 1984).

148. Obviousness is determined from the perspective of the person of ordinary skill in the art (“POSA”) at the time of the invention. 35 U.S.C. § 103(a); *see also KSR*, 550 U.S. at 420 (“The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art.”).

149. A challenger must show that the prior art teaches all elements of the invention, or else obviousness is not established. *UCB, Inc. v. Watson Lab’ys Inc.*, 927 F.3d 1272, 1286 (Fed. Cir. 2019) (upholding determination of non-obviousness).

150. “Generally, a party seeking to invalidate a patent as obvious must demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.” *In re Cyclobenzaprine*, 676 F.3d at 1068-69 (internal quotation marks omitted); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *see also Microsoft Corp. v. i4i Ltd. P’ship*, 564 U.S. 91, 95, 102-03 (2011) (discussing the clear and convincing standard).

151. “[T]he use of inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of obviousness. *Par Pharm. v. Twi Pharms.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (“[T]he concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the natural result of the combination of prior art elements.”); *see also, e.g., In re Rijckaert*, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993) (“The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish inherency].” (alteration in original)); *In re Shetty*, 566 F.2d 81, 86 (C.C.P.A. 1977) (“[T]he

inherency of an advantage and its obviousness are entirely different questions. . . . Obviousness cannot be predicated on what is unknown.” (quoting *In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966))).

152. The inherency analysis is a factual inquiry to determine whether the limitation at issue is necessarily present in the prior art. *See Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020); *Toyota Motor Corp. v. Reactive Surfaces Ltd., LLP*, 816 F. App’x 480, 483–84 (Fed. Cir. 2020) (“‘[I]n order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis,’ a party must show that ‘the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.’”) (quoting *PAR Pharm., Inc. V. TWI Pharms., Inc.*, 773 F.3d at 1195–96 (Fed. Cir. 2014)).

153. To prove obviousness, the patent challenger must demonstrate that the claimed element was necessarily present in the prior art or that a POSA would have understood it to be disclosed. *See Allergan, Inc. v. Sandoz*, 796 F.3d 1293, 1307 (Fed. Cir. 2015) (“The prior art did not disclose, either explicitly or implicitly, the claimed formulation; rather, it taught away from such a formulation. A person of ordinary skill in the art thus would not have had a reason to select the claimed formulation from the prior art ranges or to modify Lumigan 0.03% to arrive at the claimed formulation. The unexpected properties of the claimed formulation, even if inherent in that formulation, differ in kind from the prior art, thereby supporting a conclusion of nonobviousness.”); *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (“Sandoz argues that although lyophilization in the presence of mannitol produced an unexpected result, the result was ‘inevitable’ and thus ‘inherent,’ and thus not ‘inventive.’ . . . However, invention is not a matter of what the inventor intended when the experiment was performed;

obviousness is measured objectively in light of the prior art, as viewed by a person of ordinary skill in the field of the invention . . . No expert testified that they foresaw, or expected, or would have intended, the reaction between bortezomiband mannitol, or that the resulting ester would have the long-sought properties and advantages.”); *Honeywell Int’l Inc. v. Mexichem Amanco Holding*, 865 F.3d 1348, 1355 (Fed. Cir. 2017) (“What is important regarding properties that may be inherent, but unknown, is whether they are unexpected. All properties of a composition are inherent in that composition, but unexpected properties may cause what may appear to be an obvious composition to be nonobvious.”); *Merck Sharp & Dohme Corp. v. Hospira Inc.*, 221 F. Supp. 3d 497, 515 (D. Del. 2016) (“If, at the moment before invention, a voice whispered to the inventors, ‘Do you think it’ll work?’ the answer would most likely have been, ‘I don’t know.’ This is, at least in part, because neither the inventors, nor anyone else, had any understanding of the adduct’s ability to stabilize ertapenem. . . . In other words, the prior art did not teach a skilled artisan to combine ertapenem with bicarbonate/carbonate at a neutral pH. Thus, this is not a case where the prior art’s ‘express teachings render the claimed . . . formulation obvious, and the claimed [adduct] adds nothing of patentable consequence.’ . . . The adduct is not merely an inherent property of an obvious formulation. Accordingly, Defendant has failed to show that the adduct is ‘the natural result of the combination of elements explicitly disclosed by the prior art.’”).

154. The “necessarily present” standard “is an exacting standard which cannot be met by a showing of ‘probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.’” *Toyota*, 816 F. App’x at 484 (quoting *Hansgirk v. Kemmer*, 102 F.2d 212, 213 (C.C.P.A. 1939)); *see also PAR Pharm.*, 773 F.3d at 1196 (“Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.”) (quoting *Oelrich*, 666 F.2d at 581).

“‘If . . . the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient’ to render the function inherent.” *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) (quoting *Oelrich*, 666 F.2d at 581).

**b) Differences Between the Claimed Invention and the Prior Art**

155. Patent claims are not invalid as obvious under 35 U.S.C. § 103 unless “the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” It is imperative to consider how a person of ordinary skill in the art would have viewed the relevant art to ascertain whether “the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention,” 35 U.S.C. § 103; that is, to avoid the “insidious effect of a hindsight syndrome,” *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). *See KSR*, 550 U.S. at 421; *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1375 (Fed. Cir. 2011) (“Importantly, the great challenge of the obviousness judgment is proceeding without any hint of hindsight.”); *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1088 (Fed. Cir. 2008); *see In re Rouffet*, 149 F.3d 1350, 1358 (Fed. Cir. 1998); *see also MedPointe Healthcare Inc. v. Hi-Tech Pharmacal Co.*, 2006 WL 3780783, at \*4 (D.N.J. Dec. 21, 2006).

156. A finding of obviousness cannot be based upon hindsight selection of elements of the claimed invention from among the disclosures of the prior art. *E.g., In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (“It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of



ordinary skill in the art.” (quoting *In re Wesslau*, 353 F.2d 238, 2341 (C.C.P.A. 1965)); *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1294-96 (Fed. Cir. 2012). “[T]he proper analysis requires a form of amnesia that ‘forgets’ the invention and analyzes the prior art and understanding of the problem at the date of invention.” *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012); *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (“Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.”), *abrogated on other grounds*, *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). Failure to consider the prior art as a whole compels rejection of an obviousness contention. *Ortho-McNeil Pharm., Inc. v. Mylan Lab’ys., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (rejecting obviousness challenge on the basis that challenger’s expert “discounted the number and complexity of the alternatives”).

157. The Court must look to the hypothetical POSA to determine whether such a person would have been motivated to arrive at and have had a reasonable expectation of success in achieving the claimed invention. *See Eli Lilly v. Teva*, 619 F.3d at 1340 (Fed. Cir. 2010) (rejecting argument that inventors’ pursuit of raloxifene as a treatment indicates that a POSA would have a reasonable expectation of success; “the record will not allow this court to conflate Lilly scientists with those of ordinary skill in the art”) (citing *KSR*, 550 U.S. at 420); *OSI Pharms., Inc. v. Mylan Pharms., Inc.*, 858 F. Supp. 2d 341, 357, 359 (D. Del. 2012) (an inventor “comment[ing] upon and circulat[ing] a patent abstract to his colleagues . . . is not informative with respect to motivation of the hypothetical person of ordinary skill in the art”; and internal company memos discussing expectations were found insufficient to show reasonable expectation of success, as the inventors’ views “may not be indicative of those of the hypothetical person of ordinary skill in the art”). An

inventor's knowledge and efforts cannot be used to show obviousness because it would be impermissible hindsight. *Otsuka*, 678 F.3d at 1296 ("What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art."); *Life Techs., Inc. v. Clonetech Lab'ys, Inc.*, 224 F.3d, 1320, 1325-26 (Fed. Cir. 2000) (finding that it is impermissible hindsight to "us[e] the inventors' success as evidence that the success would have been expected"); *Amgen Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d at 1363 (rejecting argument that inventor's expectation that cells would produce desired protein supported obviousness case).

**c) Solution to an Unknown Problem Is Not Obvious**

158. An invention claimed in a patent is not obvious if it solves a problem that was not previously known or reasonably suggested in the art. *E.g., Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45, 67-68 (1923); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353-57 (Fed. Cir. 2013); *In re Omeprazole Pat. Litig.*, 536 F.3d 1361, 1380-81 (Fed. Cir. 2008); *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 935-36 (Fed. Cir. 2019); *Merck & Co., Inc. v. Sandoz Inc.*, No. 10-1625 (SRC)(PS), 2012 WL 266412, at \*10 (D.N.J. Jan. 30, 2012).

159. "[K]nowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method." *Innogenetics, NV v. Abbott Lab'ys*, 512 F.3d 1363, 1373-74 (Fed. Cir. 2008); *see also Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("Recognition of a need does not render obvious the achievement that meets that need. . . . Recognition of an unsolved problem does not render the solution obvious."); *Novartis Pharms. Corp. v. Watson Labs., Inc.*, 611 F. App'x 988, 995 (Fed. Cir. 2015) ("Even an obvious solution, however, does not render an invention obvious if the problem solved was previously unknown."); *id.* at 996 ("Although the addition of an antioxidant would have been an obvious solution for a formulation with known oxidation problems, here Watson failed to prove that a rivastigmine formulation was known to be susceptible

to oxidative degradation.”).

160. “The problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable. Therefore, the claimed invention would not have been obvious to try to one of ordinary skill in the art.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356–57 (Fed. Cir. 2013); *see also id.* at 1357 (“Indeed ordinary artisans would not have thought to try at all because they would not have recognized the problem.”); *Nike, Inc. v. Adidas AG*, 812 F.3d 1326, 1338 (Fed. Cir. 2016), *overruled on alternate grounds by Aqua Prods., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017) (in discussing *Leo Pharm.* stating that “[p]ersons of skill in the art cannot have tried and failed to solve the problem if they were never aware of that problem to begin with”); *see also Bayer Pharma AG v. Watson Lab’ys, Inc.*, 212 F. Supp. 3d 489, 524-25 (D. Del. 2016) (finding that where a failure of a contraceptive medication to prevent ovulation was not known in the prior art it provided support for the court’s conclusion that the patent challenger failed to meet its burden of clear and convincing evidence); *Forest Lab’ys, LLC v. Sigmapharm Lab’ys, LLC*, 918 F.3d 928, 935-36 (Fed. Cir. 2019) (upholding the district court’s finding that a cardiotoxicity issue solved by the claimed invention was not publicly known); *Janssen Pharms., Inc. v. Tolmar, Inc.*, 718 F. Supp. 3d 394, 428 (D. Del. 2024), *reconsideration denied sub nom. Pharms. v. Tolmar, Inc.*, No. CV 21-1784-WCB, 2024 WL 2972832 (D. Del. June 13, 2024) (“The claimed dosing regimen solved a ‘problem . . . not known in the art,’ and the solution to the unknown problem would not have been obvious.”); *Avanir Pharms., Inc. v. Actavis S. Atl. LLC*, 36 F. Supp. 3d 475, 506-07 (D. Del. 2014), *aff’d sub nom. Avanir Pharms. Inc. v. Par Pharm. Inc.*, 612 F. App’x 613 (Fed. Cir. 2015) (finding that the claimed invention was not obvious to try where the patent challenger “present[ed] no evidence that the ‘design need’ they identify . . . was indeed a problem in the prior art”).

**d) Motivation to Combine Prior Art**

161. “[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418; *see In re Kotzab*, 217 F.3d 1365, 1369–70 (Fed. Cir. 2000). Rather, a showing of obviousness requires proof by clear and convincing evidence that a person of ordinary skill in the art, at the time of the priority date, would have had a reason or motivation to combine references in the prior art to solve the problems in the relevant field by making the claimed invention. *See InTouch Techs., Inc. v. VGo Commc’ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014); *Unigene Lab’ys, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) (“Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a [POSA] would have selected and combined those prior art elements.”) (citation omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356–57 (Fed. Cir. 2007); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344–45 (Fed. Cir. 2000) (affirming that defendants “did not show sufficient motivation for one of ordinary skill in the art at the time of the invention to take any one of the following steps, let alone the entire complex combination”); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383 (Fed. Cir. 1986) (“Focusing on the obviousness of substitutions and differences instead of on an invention as a whole . . . was a legally improper way to simplify the difficult determination of obviousness.”); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) (It is improper to “pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.” (quoting *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965))); *Akzo N.V. v. U.S. Int’l Trade Comm’n*, 808 F.2d 1471, 1481 (Fed. Cir. 1986) (stating that

the patent challenger could not “pick and choose among individual parts of assorted prior art references ‘as a mosaic to recreate a facsimile of the claimed invention’” (quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)); see also *Ortho-McNeil*, 520 F.3d at 1364 (finding that an obviousness challenge failed where an expert “simply retraced the path of the inventor with hindsight”).

162. Reason or motivation must be assessed with respect to the actual goals and motivations in the field. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1345–46 (Fed. Cir. 2013). A patent challenger must not “import hindsight into the obviousness determination by using the invention as a roadmap to find its prior art components.” *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1337 (Fed. Cir. 2005).

163. “A reason for combining disparate prior art references is a critical component of an obviousness analysis; ‘this analysis should be made explicit.’” *InTouch Techs.*, 751 F.3d at 1351 (quoting *KSR*, 550 U.S. at 418). “It is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [claimed] elements in the way the claimed new invention does.” *Id.* This is so “because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *Id.* (quoting *KSR*, 550 U.S. at 418–19). ” “Thus, even where “all claim limitations are found in a number of prior art references, the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007) “A party seeking to invalidate a patent based on obviousness must demonstrate by clear and convincing evidence that

a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (internal quotation marks omitted); *see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006) (“[T]o establish a prima facie case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention.”); *Unigene Lab’ys., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) (“In this case, the patent claims a new composition or formulation to deliver an FDA-approved active ingredient. Thus, the claimed invention is not obvious if a person of ordinary skill would not select and combine the prior art references to reach the claimed composition or formulation.”); *In re Vaidyanathan*, 381 F. App’x 985, 993 (Fed. Cir. 2010) (factfinder must “anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references.”).

164. If the POSA would not have perceived a prior art reference to have a “disadvantage” or “problem,” the POSA would not have been motivated to modify that reference. *Winner Int’l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 (Fed. Cir. 2000) (affirming the district court’s conclusion “that there was no motivation to combine Johnson with the ratcheting mechanism of Moore because (1) there was no apparent disadvantage to the dead-bolt mechanism of Johnson, and therefore the motivation to combine would not stem from the ‘nature of the problem’ facing one of ordinary skill in the art, because no ‘problem’ was perceived”). And even if the POSA had recognized a problem, “knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method.”

*Innogenetics, N.V. v. Abbott Lab'ys.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008) (holding that it is impermissible to use “hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.”).

165. A POSA would not be motivated to implement a modification designed to address one problem if it would likely create an equal or greater problem in another area. *See Institut Pasteur*, 738 F.3d at 1346 (allegedly obvious combination would be avoided because of prior art teaching that such changes would lead to toxicity); *Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc.*, 456 F. Supp. 2d 644, 666–67 (D.N.J. 2006) (finding the POSA “would have avoided modifying [] chemical structure because such modifications are risky and uncertain” and other safer, and more conventional, routes to obtaining the desired result existed).

166. “Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.” *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017).

167. Where “a defendant urges an obviousness finding by ‘merely throw[ing] metaphorical darts at a board’ in hopes of arriving at a successful result, but ‘the prior art gave . . . no direction as to which of many possible choices is likely to be successful,’ courts should reject ‘hindsight claims of obviousness.’” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1070–71 (Fed. Cir. 2012) (quoting *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)); *see Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013).

**e) Specific Motivation to Achieve the Claimed Invention**

168. It is important that the record supply a reason, available within the knowledge of a POSA, to take particular steps or make particular modifications to achieve the claimed invention. *See KSR*, 550 U.S. at 418 (“[I]t can be important to identify a reason that would have prompted a

person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.”); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1336-37 (Fed. Cir. 2010) (methods of using compound known to have low bioavailability were not obvious where there was “no evidence from before the time of invention that would teach, suggest, or motivate or supply any common sense reason for a person of ordinary skill in the art to reject the bioavailability concerns and routinely, simply, or easily arrive at the inventive result”); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343-45 (Fed. Cir. 2000) (patent challenger’s failure to show sufficient motivation “has all the earmarks of somebody looking at this from hindsight.”); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“[I]t remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.”); *Eisai Co. Ltd. v. Dr. Reddy’s Lab’ys., Ltd.*, 533 F.3d 1353, 1358-59 (Fed. Cir. 2008); *Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993-94 (Fed. Cir. 2017)

169. Merely stating that there is a “general motivation” to develop a therapy is insufficient proof of a motivation to combine particular references. *See Innogenetics, N.V. v. Abbott Lab’ys.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008) (“[K]nowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed [invention].”); *Abbott Lab’ys. v. Sandoz, Inc.*, 544 F.3d 1341, 1351-52 (Fed. Cir. 2008); *see Corning Inc. v. SRU Biosystems*, 400 F. Supp. 2d 653, 670-71 (D. Del. 2005) (criticizing expert’s analysis where expert relied only on references selected by counsel, used the claims of the patent-in-suit to select and focus on particular disclosures of those references, and referred only to “general motivations” to combine references).



170. A motivation to investigate further is insufficient to establish obviousness. *Pfizer Inc. v. Watson Pharms., Inc.*, 920 F. Supp. 2d 552, 563 (D. Del. 2013) (finding motivation to “continue investigating rapamycin’s immunosuppressive properties, and a reasonable expectation that such properties would continue to be developed at an incremental pace,” insufficient to show that the claimed method of inhibiting transplant rejection in mammals was obvious); *Vanda Pharms. Inc. v. Roxane Lab’ys., Inc.*, 203 F. Supp. 3d 412, 426-27 (D. Del. 2016) (finding claims not obvious where, even though prior art provided a basis to study certain properties, the results were unpredictable) (citing *In re Dow Chem. Co.*, 837 F.2d at 473), *aff’d sub nom. on other grounds*, *Vanda Pharms. Inc. v. W.-Ward Pharms. Int’l Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018).

171. As the Federal Circuit has explained post-*KSR*, retracing the path of the inventor with hindsight, and discounting the number and complexity of the alternatives, is always inappropriate for an obviousness test based on the language of 35 U.S.C. § 103 that requires the analysis to examine “the subject matter as a whole” to ascertain if it “would have been obvious at the time the invention was made.” *Ortho-McNeil*, 520 F.3d at 1363–64. The Federal Circuit explained that “at the time of invention, the inventor’s insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted.” *Id.*

**f) Reasonable Expectation of Success To Achieve the Claimed Invention**

172. “[E]ven if it was obvious to experiment with [certain] options,” an invention is not obvious when “there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed.” *Leo Pharm.*, 726 F.3d at 1357. Indeed, a patent challenger must further show by clear and convincing evidence that a POSA motivated to combine the teachings of the prior art references would have had a reasonable expectation of success in doing so. *E.g.*, *In re Cyclobenzaprine*, 676 F.3d at 1068-69; *Amgen Inc. v. F. Hoffman-*

*La Roche Ltd.*, 580 F.3d 1340, 1362-63 (Fed. Cir. 2009); *Otsuka*, 678 F.3d at 1292-93; *Eli Lilly and Co. v. Teva Pharms.*, 8 F.4th 1331, 1343-44 (Fed. Cir. 2021).

173. While “predictability is a touchstone of obviousness,” predictability “refers not only to the expectation that the prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.” *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009); *Valeant Int’l (Barbados) SRL v. Watson Pharms., Inc.*, C.A. No. 10-20526, 2011 WL 6792653, at \*1, 7, 10-11 (S.D. Fl. Nov. 8, 2011) (method of treating depression with no stability limitations nonobvious because the problem in the art was instability, and defendant failed to prove a POSA would have had a reasonable expectation of increased stability), *aff’d sub nom. Valeant Int’l Bermuda v. Actavis, Inc.*, 534 F. App’x 999 (Fed. Cir. 2013).

174. “[I]t [is] not enough for the appellant-defendant to [show] that a skilled artisan would have pursued the claimed method as a treatment option, but the appellant defendant also [has] to show that the skilled artisan would have reasonably expected to achieve success in the treatment.” *Eli Lilly v. Teva Pharms.*, 8 F.4th at 1343-47 (affirming Board’s finding that despite clear reasons to combine the prior art teachings, clinical and *in vivo* data of different compounds would not have provided a reasonable expectation of success in using the claimed compounds to treat vasomotor symptoms, such as a migraine headache); *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 404 (D. Del. 2021) (two partial responses in R/R MCL patients in a phase I trial “did not teach the efficacy of ibrutinib for treating R/R MCL, and an artisan of ordinary skill could not have reasonably expected success in light of the unpredictable nature of oncology and the study’s extremely small sample size”), *aff’d sub nom. Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022).

175. “[T]o have a reasonable expectation of success, one must be motivated to do more than merely to . . . try each of numerous possible choices until one possibly arrived at a successful result.” *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017) (alteration in original).

176. The Federal Circuit considers the potential harm and safety concerns of methods in determining whether they were obvious regardless of whether the claims contain safety limitations. *Eli Lilly v. Actavis Elizabeth*, 435 F. App’x at 919-21 (method of treatment using an “effective” amount of a drug not obvious where the prior art reported that a similar compound caused death in children, and there was no evidence that the claimed treatment would be “devoid of the negative effects of known and similar products”); *see also Novartis Pharms. Corp. v. Breckenridge Pharm., Inc.*, 248 F. Supp. 3d 578, 590-91, 593, 594 (D. Del. 2017) (method of treatment by co-administering synergistically effective amounts of two drugs nonobvious where there was no evidence that the combination would be safe for humans in light of each drug’s known toxicities), *rev’d on other grounds by*, 909 F.3d 1355 (Fed. Cir. 2018).

177. To prove a reasonable expectation of success, “[i]t is not sufficient to merely assert an ‘obvious-to-try theory,’ especially where . . . the relevant art is littered with a history of inconsistent clinical trial results.” *Sanofi v. Glenmark Pharms. Inc.*, 204 F. Supp. 3d 665, 696 (D. Del. 2016) (citing *In re Cyclobenzaprine*, 676 F. 3d at 1072–73) (finding that “while a POSA may have been motivated to try” the claimed method of treatment based on the prior art, “a POSA . . . would not have had a reasonable expectation of success, given what was known” in the art). “Evidence of obviousness, especially when that evidence is proffered in support of an ‘obvious-to-try’ theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were ‘finite,’ ‘small,’ or ‘easily traversed,’ and that skilled artisans would have had a reason to select the route that produced the claimed invention.” *In re Cyclobenzaprine*, 676 F.3d

at 1072.

178. “[O]bvious to try” is not to be equated with obviousness under 35 U.S.C. § 103.” *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990) (citing cases). A challenger can establish that the POSA would have had a reason to make the claimed invention on the basis that it was “obvious to try” if (1) “there are a finite number of identified, predictable solutions” and (2) those predictable solutions “lead[] to the anticipated success.” *KSR*, 550 U.S. at 421. Thus, the challenger must show that “the possible options skilled artisans would have encountered were ‘finite,’ ‘small,’ or ‘easily traversed,’ and that skilled artisans would have had a reason to select the route that produced the claimed invention.” *Cyclobenzaprine*, 676 F.3d at 1072.

179. Statements from the prior art must be read in the proper context when determining whether a POSA would have had a reasonable expectation of success; a hope that a drug will work or a hypothesis that requires further testing does not support a reasonable expectation of success. *See OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1384–85 (Fed. Cir. 2019); *Sanofi-Aventis U.S. LLC v. Sandoz, Inc.*, No. CV 20-804-RGA, 2023 WL 4175334, at \*14 (D. Del. June 26, 2023) (Plaintiff’s expert “was able to list a variety of cancer drugs that failed at Phase III. Therefore, [the court did] not think a POSA would reasonably extrapolate from the fact that a Phase III trial had begun that a drug could be expected to be successful.”), *appeal dismissed*, No. 2023-2264, 2023 WL 6532673 (Fed. Cir. Oct. 6, 2023). “[C]autious optimism is not sufficient.” *Sanofi*, 875 F.3d at 650. “[N]or is ‘hope.’” *OSI Pharms.*, 939 F.3d at 1385. “While I think the prior art clearly provides for hope and even cautious optimism, I do not think, based on the experts’ testimony, that it supports the higher bar of a reasonable expectation of success.”); *Sanofi v. Watson Lab’ys*, 875 F.3d 636, 641, 646-50 (Fed. Cir. 2017) (finding no reasonable expectation of success even though the prior art disclosed a study’s “rationale and design” because a POSA “would have been at best

cautiously optimistic that dronedarone could reduce the risk of cardiovascular hospitalization.”); *Novartis Pharms. Corp. v. W.-Ward Pharms. Int’l Ltd.*, 923 F.3d 1051, 1061 (Fed. Cir. 2019) (no reasonable expectation of success based on evidence including phase I results).

180. “There can be little better evidence negating a reasonable expectation of success than actual reports of failure.” *In re Cyclobenzaprine*, 676 F.3d at 1081 (quoting *Boehringer Ingelheim Vetmedica, Inc. v. Schering–Plough Corp.*, 320 F.3d 1339, 1354 (Fed.Cir.2003)).

181. Ongoing trials do not raise a POSA’s expectation past “hope” or “cautious optimism” to support a reasonable expectation of success, particularly in a field where there is substantial unpredictability and where there have been numerous failed trials. *Sanofi-Aventis US LLC v. Sandoz, Inc.*, No. CV 20-804-RGA, 2023 WL 4175334, at \*9 (D. Del. June 26, 2023) (“The existence of the [ongoing] TROPIC trial would have bolstered a POSA's cautious optimism, but would not have provided enough concrete information to take a POSA beyond cautious optimism.”); *see also id.* at \*14 (“I also do not think that the mere existence of a Phase III trial, with no information about its results, would have lifted a POSA's hopes over the bar for a reasonable expectation of success.”); *Novartis Pharms. Corp. v. W.-Ward Pharms. Int’l Ltd.*, 287 F. Supp. 3d 505, 516-17 (D. Del. 2017) (discounting the existence of a phase II study where no data was available). Clinical trials do not always provide a POSA with a reasonable expectation of success. *See Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 648,650 (Fed. Cir. 2017) (finding that where clinical trial publications suggested the benefits observed in the trials were “potential” they did not support a finding of a reasonable expectation of success); *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1383 (Fed. Cir. 2019) (overturning the district court’s finding that there was a reasonable expectation of success based on prior art disclosures and the fact that the drug of interest had entered Phase II clinical trials).

**g) Objective Indicia of Non-Obviousness**

182. “A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion of obviousness until all those factors are considered.” *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (*en banc*).

183. “Once a *prima facie* case of obviousness has been established, the burden shifts to the applicant to come forward with evidence of nonobviousness to overcome the *prima facie* case.” *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996).

184. Objective indicia, such as long-felt but unmet need, failure of others, and unexpected results can serve as probative, independent evidence of nonobviousness. *KSR*, 550 U.S. at 406; *Ortho-McNeil*, 520 F.3d at 1365 (Objective evidence “is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness.”).

185. “Objective indicia of nonobviousness play a critical role in the obviousness analysis. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quoting *Ortho–McNeil Pharm., Inc. v. Mylan Lab ’ys., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008)). “They are ‘not just a cumulative or confirmatory part of the obviousness calculus but constitute[ ] independent evidence of nonobviousness.’” *Id.* (alteration in original).

186. Objective evidence such as unexpected results, failure of others, long-felt but unmet need, commercial success, and industry praise must be considered before a conclusion on obviousness is reached. *Ortho–McNeil Pharm., Inc. v. Mylan Lab ’ys., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (“[T]his evidence is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness.”); *Hybritech*, 802 F.2d at 1380 (“Objective evidence . . . is not merely ‘icing on the cake.’”); *In re Cyclobenzaprine Hydrochloride*

*Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (holding that the district court erred by determining that the patents were obvious before considering the objective evidence of nonobviousness).

187. The objective indicia of nonobviousness, the fourth Graham factor, “may often be the most probative and cogent evidence” available. *Ortho-McNeil Pharm., Inc. v. Mylan Lab’ys, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1305 (Fed. Cir. 2010). *Crocs, Inc. v. Int’l Trade Comm’n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010); *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579 (Fed. Cir. 1997). The objective indicia of nonobviousness “guard as a check against hindsight bias,” *In re Cyclobenzaprine*, 676 F.3d at 1079, and “provide objective evidence of how the patented device is viewed in the marketplace, by those directly interested in the product,” *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988).

188. “Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application.” *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (relying on results of studies conducted after the filing date to find unexpected results because “[t]here is no requirement that an invention’s properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack.”); see *In re Zenitz*, 333 F.2d 924, 927-28 (C.C.P.A. 1964).

189. A fact-finder “must withhold judgment on an obviousness challenge until it considers all relevant evidence, including that relating to the objective considerations.” *In re*

*Cyclobenzaprine*, 676 F.3d at 1079. “This objective evidence must be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.” *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (internal quotation marks omitted).

190. It is error to reach a conclusion on obviousness before objective indicia of nonobviousness are evaluated. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016).

(1) Teaching away

191. All teachings in the prior art must be considered in the obviousness determination, including those which might lead away from the claimed invention. *In re Dow Chem. Co.*, 837 F.2d at 473 (“[T]he full field of the invention must be considered.”); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987); *Warner Chilcott Co., LLC v. Lupin Ltd.*, No. 11-5048, 2014 WL 202659, at \*9 (D.N.J. Jan. 17, 2014), *aff’d*, 580 F. App’x 911 (Fed. Cir. 2014).

192. If the prior art “teaches away” from the invention rather than motivating the POSA to do what the patentee has done, the invention is nonobvious. *DePuy Spine*, 567 F.3d at 1326. “An inference of nonobviousness is especially strong where the prior art’s teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.” *Id.* A prior art reference that teaches away “alone can defeat [an] obviousness claim.” *Winner Int’l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349–50 (Fed. Cir. 2000).

193. “Whether prior art teaches away or toward a claimed invention is a finding of fact that is a ‘subsidiary requirement’ of the ‘scope and content of the prior art.’” *Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 369-70 (D.N.J. 2009), *aff’d sub nom.*, *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346 (Fed. Cir. 2010); *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015).

194. “A reference may be said to teach away when a person of ordinary skill, upon



reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant[.]” *DePuy Spine*, 567 F.3d at 1327, or “if it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant,” *Tec Air, Inc. v. Denso Mfg. Mich., Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). *See also Pozen Inc. v. Par Pharm. Inc.*, 696 F.3d 1151, 1164-65 (Fed. Cir. 2012) (affirming finding that a prior art reference taught away from using the claimed combination of drugs to treat migraines when the reference taught that there was only one effective treatment); *Allergan*, 796 F.3d at 1305-06 (finding the prior art taught away from a claimed formulation which contained a high concentration of a certain preservative, where the prior art taught that the concentration of the preservative should be minimized due to increased side effects and the invention was directed toward a lifelong drug); *Unigene Lab’ys.*, 655 F.3d at 1361; *Crocs, Inc. v. Int’l Trade Comm’n*, 598 F.3d 1294, 1308–09 (Fed. Cir. 2010) (explaining that criticisms of patent challenger’s proposed modification taught away from claimed invention).

195. “‘Teaching away’ does not require that the prior art foresaw the specific invention that was later made, and warned against taking that path. It is indeed of interest if the prior art warned against the very modification made by the patentee, but it is not the sole basis on which a trier of fact could find that the prior art led away from the direction taken by the patentee.” *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1343 (Fed. Cir. 2011) (explaining that a jury could find that prior art taught away from one solution because all prior art taught a different solution), *abrogated on other grounds by Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923 (2016).

196. The reference need not address an aspect of the invention recited specifically in the

claim to teach away. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1345–46 (Fed. Cir. 2013) (a prior art suggestion that a reference would cause toxicity to cells precluded obviousness irrespective of whether claims recited lack of toxicity).

197. Prior art references cannot be combined if one of the references teaches away from its combination with another. *See Tec Air*, 192 F.3d at 1360 (“There is no suggestion to combine [references] . . . if a reference teaches away from its combination with another source.”).

198. Prior art references that do not rise to the level of “teaching away” can nonetheless demonstrate an absence of a motivation to combine references. *See Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018); *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1051 n.15 (Fed. Cir. 2016) (*en banc*) (“[E]ven if [the reference] does not teach away, its statements regarding users preferring other forms of switches are relevant to a finding regarding whether a skilled artisan would be motivated to combine [the references].”). The burden remains on the patent challenger to identify a motivation to combine a reference with other references, regardless of whether the reference teaches away or not. *See Rembrandt Wireless Techs., LP v. Samsung Elecs. Co.*, 853 F.3d 1370, 1379–80 (Fed. Cir. 2017) (“[T]he absence of a formal teaching away in one reference does not automatically establish a motivation to combine it with another reference in the same field.”).

## (2) Unexpected results

199. Results or properties of the claimed invention that would have been surprising or unexpected to a POSA can be used as evidence of non-obviousness. *Kao Corp. v. Unilever U.S. Inc.*, 441 F.3d 963, 968-70 (Fed. Cir. 2006) (affirming trial court’s finding of nonobviousness based on unexpected results of a claimed method for removing keratotic plugs from skin). “One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of ‘unexpected results.’” *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995); *see also Millennium Pharms.*

*v. Sandoz, Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017). Whether a result is unexpected is a question of fact. *Id.* at 749. The relevant time period for the “unexpected results” inquiry is whether the results would have been unexpected by one of ordinary skill in the art at the time of the patentee’s application and based on knowledge available at that time. *See, e.g., Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014). Results or properties of the claimed invention that would have been surprising or unexpected to a POSA can be used as evidence of non-obviousness. *Kao Corp. v. Unilever U.S. Inc.*, 441 F.3d 963, 968-70 (Fed. Cir. 2006) (affirming trial court’s finding of nonobviousness based on unexpected results of a claimed method for removing keratotic plugs from skin).

200. The patentee may offer evidence of unexpected results even if that evidence was obtained after the patent’s filing or issue date. *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011); *In re Chu*, 66 F.3d 292, 299 (Fed. Cir. 1995) (“We have found no cases supporting the position that a patent applicant’s evidence and/or arguments traversing a § 103 rejection must be contained within the specification”).

201. Failure in other drugs can support a finding of “unexpected results.” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306–07 (Fed. Cir. 2015) (holding “the district court did not clearly err in finding that the claimed formulation exhibited ‘unexpected results’” when the “results exhibited by the claimed formulation thus constitute an unexpected difference in kind, *viz.*, the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment.”); *Leo Pharms. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (reversing the obviousness finding by Board of Patent Appeals and Interferences because “extensive experimental evidence” that previous formulations containing the two active

ingredients all showed “significant degradation,” were “a strong indication that the ’013 patent’s combination of known elements yields more than just predictable results”).

202. “Unexpected results are useful to show the ‘improved properties provided by the claimed compositions are much greater than would have been predicted.’” *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quoting *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995)). The basic principle that underlies an unexpected results analysis is “that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.” *Soni*, 54 F.3d at 750. Unexpected results that inherently flow from the claimed invention are evidence of nonobviousness and need not be described or proven in the patent specification. See *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (holding that later-developed evidence of unexpected results is relevant to nonobviousness).

203. The patent challenger has the burden of proving that none of the properties of the claimed invention were unexpected. See *Am. Hosp. Supply Corp. v. Travenol Lab’ys., Inc.*, 745 F.2d 1, 8 (Fed. Cir. 1984) (“[Patent holder] is under no compulsion either to prove a new and surprising result . . . . Rather, the burden was on [challenger] to establish the lack of new and surprising results or the lack of criticality.”).

### (3) Commercial success

204. “When a patentee can demonstrate commercial success,” which is “usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention.” See *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997).

205. If a patent challenger wishes to rebut the nexus between the commercial success and the claimed invention, the “patent challenger cannot successfully rebut the presumption” of nexus “with argument alone—it must present evidence.” *Polaris Indus., Inc. v. Arctic Cat, Inc.*,

882 F.3d 1056, 1072 (Fed. Cir. 2018).

206. In order for marketing to rebut a finding of nexus, the commercial success needs to be “the calculated result of an aggressive marketing campaign of *unprecedented* scope.” *Cadence Pharms., Inc. v. Exela Pharma Scis., LLC*, No. CV 11-733-LPS, 2013 WL 11083853, at \*30 (D. Del. Nov. 14, 2013) (emphasis in original); *see also Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, No. CV 2:18-00734, 2024 WL 5135666, at \*26 (D.N.J. Dec. 17, 2024) (promotional spending and discounts in line with competitors did not defeat nexus). Further, while marketing can make potential purchasers “aware” of products, it “does not make these potential users buy them; the products have to work.” *Hybritech*, 802 F.2d at 1382.

207. While commercial success is typically demonstrated by “significant sales in a relevant market,” *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997), market share can be further supportive evidence. *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021), *cert. denied*, 142 S. Ct. 1418 (2022); *see also Exeltis USA, Inc. v. Lupin Ltd.*, 2024 4040470, at \*31-33 (D. Del. Sept. 4, 2024) (finding commercial success “based on a combination of market share and sales” and presumption of nexus was un rebutted).

208. “[A]s a theoretical matter, a blocking patent may or may not deter innovation in the blocked space by commercially motivated potential innovators other than the owners or licensees of the blocking patent.” *Acorda Therapeutics, Inc. v. Roxane Lab’ys., Inc.*, 903 F.3d 1310, 1338 (Fed. Cir. 2018). As such “the magnitude of the diminution in incentive in any context—in particular, whether it was great enough to have actually deterred activity that otherwise would have occurred—is ‘a fact-specific inquiry.’” *Id.* at 1339 (quoting *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 731 (Fed. Cir. 2017))

209. “Besides the assessment of whether the blocking patent can be successfully challenged, a number of variables appear generally relevant to the calculus, including: the costliness of the project; the risk of research failure; the nature of improvements that might arise from the project, and whether such improvements will be entirely covered by the blocking patent; the size of the market opportunities anticipated for such improvements; the costs of arriving at the improvements and getting them to market; the risk of losing the invention race to a blocking-patent owner or licensee; the risk that the blocking-patent owner (making its own economic calculations, perhaps in light of its own other products or research activities) will altogether refuse to grant a license to the improvement or will demand so large a share of profits that the whole project is not worthwhile for the potential innovator—all evaluated in light of other investment opportunities.” *Id.* at 1338. Evidence that a competitor was incentivized to and invested resources in developing a competing product favors finding that an alleged blocking patent did not deter development. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, No. CV 2:18-00734, 2024 WL 5135666, at \*29 (D.N.J. Dec. 17, 2024).

210. Regulatory exclusivity and blocking patents are not the same. *See Pfizer Inc. v. Teva Pharms. USA, Inc.*, 460 F. Supp. 2d 650, 654 (D.N.J. 2006). In fact, courts have “previously found evidence of commercial success to be probative in cases where the drug at issue was still enjoying the benefits of the five year exclusivity period.” *Id.*

(4) Industry praise

211. “Evidence that the industry praised a claimed invention or a product that embodies the patent claims weighs against an assertion that the same claimed invention would have been obvious.” *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (*en banc*); *see also WBIP*, 829 F.3d at 1335 (finding that awards received by the patentee is “strong evidence of industry recognition of the significance and value of the claimed invention” and “weighs in favor

of nonobviousness”); *see also id.* at 1334 (“[I]f there is evidence of industry praise in the record, it weighs in favor of the nonobviousness of the claimed invention.”); *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) (“[I]ndustry praise . . . provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected [the claimed invention].”).

212. “Industry participants, especially competitors, are not likely to praise an obvious advance over the known art.” *Apple v. Samsung*, 839 F.3d at 1053; *see also Genzyme Corp. v. Dr. Reddy’s Lab’ys., Ltd.*, Nos. 13-1506-GMS, 13-1508-GMS, 2016 WL 2757689, at \*15 (D. Del. May 11, 2016) (determining that awards bestowed on the claimed invention is recognition of “widespread praise in the US and Europe and this weighs in favor of nonobviousness”); *Pfizer Inc. v. Mylan Pharms. Inc.*, 71 F. Supp. 3d 458, 476 (D. Del. 2014) (finding that the claimed invention “was a breakthrough in the industry, widely praised by researchers and doctors”), *aff’d*, 628 F. App’x 764 (Fed. Cir. 2016); *Reseach. Found. of State Univ. of N.Y. v. Mylan Pharms. Inc.*, 723 F. Supp. 2d 638, 653 (D. Del. 2010) (noting that inter alia, industry praise for the invention is “strong evidence of secondary indicia of non-obviousness”). “Appreciation by contemporaries skilled in the field of the invention is a useful indicator of whether the invention would have been obvious to such persons at the time it was made.” *Vulcan Eng’g Co. v. Fata Aluminium, Inc.*, 278 F.3d 1366, 1373 (Fed. Cir. 2002).

#### (5) Skepticism

213. “Evidence of industry skepticism is a question of fact that weighs in favor of non-obviousness.” *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019).

214. A finding of skepticism does not require that the result be “‘technically infeasible,’ ‘unworkable,’ or ‘impossible.’” *Id.* at 1378. Rather, a showing that a relevant third party was “‘worried” about whether the claimed result would come about can support a finding of skepticism.

*Id.* (quoting *Cir. Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1337 (Fed. Cir. 2015)).

215. “If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness.” *WBIP*, 829 F.3d at 1335.

216. “[P]roceeding against accepted wisdom is evidence of nonobviousness.” *See Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 958 (Fed. Cir. 1997) (citing *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986)).

(6) Failure of others

217. Evidence that other skilled artisans have “‘tried for a long time’ to develop the claimed invention but found it ‘very hard’ and ‘were all not successful,’” can support a finding of non-obviousness.” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1082 (Fed. Cir. 2012) (quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000)); *In re Rosuvastatin Calcium Pat. Litig.*, 703 F.3d 511, 517-18 (affirming the nonobviousness of a chemical compound where, inter alia, other pharmaceutical companies had “abandoned their research . . . on the prevailing belief that pyrimidine-based statins were not promising leads to improved products”); *Knoll Pharm. Co.*, 367 F.3d at 1385 (reversing the grant of summary judgment of invalidity because the district court failed to properly consider evidence of the failure of two pharmaceutical companies to obtain FDA approval for similar drugs); *In re Cyclobenzaprine*, 676 F.3d at 1082 (reversing an invalidity judgment and holding that the district court erred when it disregarding evidence of failure of others. That the failed party had a second goal of decreasing side effects did not impact the analysis when both the failed and successful parties “share[d] a central common goal” of a therapeutically effective drug,); *Eli Lilly and Co. v. Sicor Pharms., Inc.*, 705 F. Supp. 2d 971, 1001 (S.D. Ind. 2010) (“As these researchers’ repeated unsuccessful attempts to synthesize gemcitabine demonstrate, the person of ordinary skill



in the art did not and would not have known how to synthesize gemcitabine.”); *Forest Lab ’ys., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1269 (Fed. Cir. 2007) (finding prior failure to purify the relevant enantiomer of a drug was evidence of nonobviousness).

(7) Long-felt but unsolved needs

218. “The existence of a long-felt but unsolved need that is met by the claimed invention is . . . objective evidence of non-obviousness.” *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017). “Recognition of [a] need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness.” *In re Dow*, 837 F.2d at 472; *see also In re Cyclobenzaprine*, 676 F.3d at 1082 (“Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand.”); *Minn. Mining & Mfg.*, 976 F.2d at 1574 (finding that a long-felt but unmet need can be “established by the attempts and failures of the major players in the . . . field”).

219. “If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence—the kind that can’t be bought from a hired expert, the kind that does not depend on fallible memories or doubtful inferences—of the state of knowledge.” *In re Mahurkar Double Lumen Hemodialysis Catheter Patent Litig.*, 831 F. Supp. 1354, 1378 (N.D. Ill. 1993) (citing *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1574-75 (Fed. Cir. 1992)), *aff’d*, 71 F.3d 1573 (Fed. Cir. 1995) ; *Leo Pharm. Prods., Ltd.*, 726 F.3d at 1359 (“The record also shows evidence of *long* felt but unsolved need . . . . The intervening time between the prior art’s teaching of the components and the eventual preparation of a successful composition speaks volumes to the nonobviousness of the [patent-at-issue].” (emphasis in original)); *WBIP*, 829 F.3d at 1332 (“Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious.”).

220. The presence of a long-felt but unmet need is assessed as of the time the invention was made, in view of “the date of an articulated identified problem and evidence of efforts to solve that problem.” *WBIP*, 829 F.3d at 1334; *Tex. Instruments Inc. v. U.S. Int’l Trade Comm’n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). It is “incorrect[]” to analyze long-felt need “only as of the date of the ‘most pertinent’ prior art references.” *Tex. Instruments*, 988 F.2d at 1177, 1178 (nonobviousness finding of a patented process reduced to practice in 1963 supported by a long-felt need beginning in 1957 for a process to mass produce inexpensive transistors by packaging components in plastic without damaging the devices).

221. Evidence of an enduring and unmet need has supported nonobviousness holdings for drugs addressing conditions lacking effective treatments and where existing treatments were inadequate. *Procter & Gamble*, 566 F.3d at 998 (affirming a finding of long-felt need because “osteoporosis was recognized as a serious disease and existing treatments were inadequate”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) (finding existence of “long-felt need for a safer, less toxic, and more effective” antipsychotic); *Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc.*, 456 F. Supp. 2d 644, 649, 670 (D.N.J. 2006) (finding long-felt need existed for safe antipsychotic not associated with the “serious side effects” of the other approved antipsychotic drugs); *Ortho-McNeil Pharm., Inc. v. Mylan Lab’ys., Inc.*, 348 F. Supp. 2d 713, 758 (N.D. W. Va. 2004) (finding a long-felt need for a broad-spectrum drug to treat respiratory infections where the effectiveness of the current agents against certain classes of pathogens was inadequate); *In re Cyclobenzaprine*, 676 F.3d at 1080, 1082-83; *see also Sanofi v. Glenmark*, 204 F. Supp. 3d at 695 (finding there was a long-felt need for the claimed method of treatment, even with other drugs of the same class on the market because “[i]t ha[d] been notoriously difficult to develop a drug with high efficacy . . . with a favorable side effect profile”);

*Leo Pharm. Prods., Ltd. v. Rea*, 726 F. 3d 1346, 1358 (Fed. Cir. 2013) (“While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness.”). “Recognition of [a] need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness.” *In re Dow*, 837 F.2d at 472; *see also In re Cyclobenzaprine*, 676 F.3d at 1082 (“Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand.”); *Minn. Mining & Mfg.*, 976 F.2d at 1574 (finding that a long-felt but unmet need can be “established by the attempts and failures of the major players in the . . . field”).

(8) Copying

222. Copying the patented invention is also evidence of non-obviousness. *Forest Lab’ys., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 496 (D. Del. 2006) (“The success of Lexapro® and its benefits compared to other SSRIs is also supported by the efforts of generic drug manufacturers, including Defendants to copy the claimed invention.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007); *Janssen*, 456 F. Supp. 2d at 671 (finding copying based on multiple ANDAs filed with the FDA to market generic versions of the patented drug).

223. “Copying may indeed be another form of flattering praise for inventive features . . . and thus evidence of copying tends to show nonobviousness.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1336 (Fed. Cir. 2016). “Copying the claimed invention, rather than one within the public domain, is indicative of non-obviousness.” *Windsurfing Int’l, Inc. v. AMF, Inc.*, 782 F.2d 995, 1000 (Fed. Cir. 1986); *see also Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed. Cir. 1988).

(9) Nexus

224. “[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘is the

invention disclosed and claimed in the patent.” *WBIP*, 829 F.3d at 1329 (citing *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *Crocs, Inc. v. Int’l Trade Comm’n*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010); *Demaco*, 851 F.2d at 1392-94; *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020).

225. A nexus is presumed “[w]hen the thing that is commercially successful is . . . coextensive with the patented invention,” but a patentee is “not required to prove as part of its prima facie case that the commercial success of the patented invention is *not* due to factors other than the patented invention.” *Demaco*, 851 F.2d at 1392-94 (“It is sufficient to show that the commercial success was of the patented invention itself.”). Because “there is rarely a perfect correspondence between the claimed invention and the product,” the Federal Circuit has “never held that the existence of one or more unclaimed features, standing alone, means nexus may not be presumed.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373-74 (Fed. Cir. 2019); *see also Fox Factory, Inc. v. SRAM, LLC*, 813 F. App’x 539, 542-43 (Fed. Cir. 2020) (affirming finding of coextensiveness when the features contributing to an invention’s success were “to some extent incorporated” into a claim limitation); *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202 (Fed. Cir. 2023) (“A patent owner is entitled to a presumption of nexus when it shows that the asserted objective evidence is tied to a specific product that ‘embodies the claimed features, and is coextensive with them.’”).

226. Objective evidence of nonobviousness must be commensurate in scope with the claims, but “absolute identity” is not required. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308–09 (Fed. Cir. 2011); *see also id.* (“[A] rigid requirement of absolute identity ... would defy the mandate of § 103 requiring consideration of the claimed ‘subject matter as a whole.’” (quoting 35 U.S.C. § 103)).

227. “[A] patent challenger cannot successfully rebut the presumption [of nexus] with argument alone—it must present evidence.” *WBIP*, 829 F.3d at 1329.

228. “A finding that a presumption of nexus is inappropriate does not end the inquiry into secondary considerations.” *Fox Factory*, 944 F.3d at 1373. “To the contrary, the patent owner is still afforded an opportunity to prove nexus by showing that the evidence of secondary considerations is the ‘direct result’ of the unique characteristics of the claimed invention.” *Id.* at 1773-74

229. Nexus may exist as long as it can be shown that the praise, success, or other objective evidence is due at least in part to the claimed invention. *See Apple, Inc. v. Int’l Trade Comm’n*, 725 F.3d 1356, 1366 (Fed. Cir. 2013) (finding that Apple presented “compelling secondary considerations evidence,” including industry praise received “in part” because of the claimed invention). If success is due to both claimed and unclaimed features, the patent challenger has the burden to disprove that the claimed invention contributes to the success of the invention. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1378 (Fed. Cir. 2000).

230. “It is not necessary . . . that the patented invention be solely responsible for the [objective indicia], in order for this factor to be given weight.” *Cont’l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991). “[T]he challenged patent, which covers the claimed invention at issue, cannot act as a blocking patent,” instead the blocking patent is “in place before the claimed invention.” *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1379 (Fed. Cir. 2021). “[T]he challenged patent, which covers the claimed invention at issue, cannot act as a blocking patent,” instead the blocking patent is “in place before the claimed invention.” *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1379 (Fed. Cir. 2021).

**6. Validity Under 35 U.S.C. § 112**

**a) Indefiniteness**

231. “Claim indefiniteness is a legal conclusion, in implementation of 35 U.S.C. § 112.” *Vascular Sols. LLC v. Medtronic, Inc.*, 117 F.4th 1361, 1369 (Fed. Cir. 2024) (quoting *Nature Simulation Sys. Inc. v. Autodesk, Inc.*, 50 F.4th 1358, 1361 (Fed. Cir. 2022)).

232. “United States patents are accompanied by a presumption of validity, 35 U.S.C. § 282, and invalidity must be established by clear and convincing evidence.” *Vascular Sols.*, 117 F.4th at 1369 (quoting *Nature Simulation Sys.*, 50 F.4th at 1361) (addressing indefiniteness).

233. “The claims of a patent ‘must be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them.’” *Vascular Sols.*, 117 F.4th at 1369 (internal quotation marks and alterations omitted).

234. “Patent claims are viewed and understood in light of the specification, the prosecution history, and other relevant evidence, as ‘would have allowed a skilled artisan to know the scope of the claimed invention with reasonable certainty.’” *Nature Simulation Sys.*, 50 F.4th at 1364 (quoting *Sonix Tech. Co. v. Publ’ns Int’l, Ltd.*, 844 F.3d 1370, 1376 (Fed. Cir. 2017)). “One must bear in mind, moreover, that patents are not addressed to lawyers, or even to the public generally, but rather to those skilled in the relevant art.” *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014) (internal quotation marks omitted). Accordingly, “[c]laim definiteness is analyzed ‘not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.’” *Energizer Holdings, Inc. v. Int’l Trade Comm’n*, 435 F.3d 1366, 1370 (Fed. Cir. 2006) (quoting *In re Moore*, 439 F.2d 1232, 1235 (CCPA 1971)).

235. “Because language is limited,” the Federal Circuit has “rejected the proposition that claims involving terms of degree are inherently indefinite. Thus, ‘a patentee need not define his

invention with mathematical precision in order to comply with the definiteness requirement.”  
*Sonix Tech.*, 844 F.3d at 1377 (internal citation omitted, quoting *Invitrogen*, 424 F.3d at 1384 (Fed. Cir. 2005)).

236. “The claims set forth the metes and bounds of the invention; they are not intended to repeat the detailed operation of the method as described in the specification.” *Nature Simulation Sys.*, 50 F.4th at 1366 (Fed. Cir. 2022).

**b) Written description**

237. The specification of a patent must “contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same.” 35 U.S.C. § 112(a).

238. “A specification adequately describes an invention when it reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Allergan USA, Inc. v. MSN Lab’ys Priv. Ltd.*, 111 F.4th 1358, 1373 (Fed. Cir. 2024) (internal quotation marks omitted).

239. “Written description asks whether that which is claimed is adequately described.” *In re Entresto*, 125 F.4th 1090, 1098 (Fed. Cir. 2025). The test for reasonably conveying possession of an invention is a flexible one, “requir[ing] an objective inquiry into the four corners of the specification from the perspective of a [POSA].” *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 127 F.4th 896, 914 (Fed. Cir. 2025) (internal quotation marks and citation omitted).

240. “The written description question is to be answered from the perspective of a person of ordinary skill in the art.” *Allergan USA v. MSN Lab’ys*, 111 F.4th at 1377; *see also Immunex Corp.*, 964 F.3d at 1063 (Fed. Cir. 2020) (“Written description is a question of fact, judged from the perspective of one of ordinary skill in the art as of the relevant filing date.” (citation omitted)).

241. “As the ‘hallmark’ of written description, the disclosure must be considered as a

whole, as the person of ordinary skill in the art would read it, to determine if it *reasonably* conveys possession.” *Allergan USA v. MSN Lab ’ys*, 111 F.4th at 1375 (emphasis original, citation omitted). Accordingly, the specification “need not include information that is already known and available to the experienced public.” *Zoltek Corp. v. United States*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (quoting *Space Sys./Loral, Inc. v. Lockheed Martin Corp.*, 405 F.3d 985, 987 (Fed. Cir. 2005)). An inventor must merely convey “with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (emphasis omitted); *see also Zoltek*, 815 F.3d at 1308 (“The [written description] requirement is applied in the context of the state of knowledge at the time of the invention.”). Thus, “a patentee may rely on information that is well-known in the art for purposes of meeting the written description requirement, because the specification is viewed from the perspective of one of skill in the relevant art.” *Ajinomoto Co. v. Int’l Trade Comm’n*, 932 F.3d 1342, 1359 (Fed. Cir. 2019) (internal quotation marks omitted).

242. “[I]nvalidity for lack of written description” must be demonstrated “by clear and convincing evidence.” *Forest Lab ’ys, LLC v. Sigmapharm Lab ’ys, LLC*, 918 F.3d 928, 938 (Fed. Cir. 2019); *Ajinomoto Co.*, 932 F.3d at 1352; *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1351 (Fed. Cir. 2011). The Federal Circuit has held that the test for showing written description is flexible, written description “requires an objective inquiry into the four corners of the specification from the perspective of a [POSA].” *Regeneron*, 127 F.4th at 914 (internal quotation marks and citation omitted); *see also Nalpropion Pharms., Inc. v. Actavis Lab ’ys FL, Inc.*, 934 F.3d 1344, 1351 (Fed. Cir. 2019) (“Rigidity should yield to flexible, sensible interpretation.”). “The [written description] requirement is applied in the context of the state of



knowledge at the time of the invention.” *Zoltek Corp.*, 815 F.3d at 1308. The specification therefore “need not include information that is already known and available to the experienced public.” *Id.* (quoting *Space Sys.*, 405 F.3d at 987).

243. The Federal Circuit has explicitly rejected the “characterization . . . of the court’s written description doctrine as a ‘super enablement’ standard for chemical and biotechnology inventions.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010). The POSA must merely have a basis “to recognize that the inventor invented what is claimed.” *Id.* at 1351.

244. Importantly, “‘a specification’s focus on one particular embodiment or purpose cannot limit the described invention where that specification expressly contemplates other embodiments or purposes.’” *Centrak, Inc. v. Sonitor Techs., Inc.*, 915 F.3d 1360, 1366 (Fed. Cir. 2019) (quoting *ScriptPro LLC v. Innovation Assocs., Inc.*, 833 F.3d 1336, 1341 (Fed. Cir. 2016)). “An applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.” *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (internal quotation marks and alterations omitted) (quoting *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1344 (Fed. Cir. 2001)). Consistent with that principle, “a patent claim is not necessarily invalid for lack of written description just because it is broader than the specific examples disclosed.” *Martek Bioscis. Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1371 (Fed. Cir. 2009).

245. “Claims deserve the provisional application’s earlier filing date so long as that application contains adequate written description under 35 U.S.C. § 112.” *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1371 (Fed. Cir. 2011).

246. “The ‘written description’ requirement states that the patentee must describe the

invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.” *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (alteration omitted) (quoting *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005)). Thus, the specification satisfies the written description requirement if a POSA would find it “reasonably clear what the invention is and that the patent specification conveys that meaning.” *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *see also Vas-Cath*, 935 F.2d at 1563–64. There is no requirement to “specifically mention a limitation that later appears in the claims;” such an omission “is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented.” *All Dental Prodx*, 309 F.3d at 779.

247. A claim need not be reduced to practice, nor explicitly exemplified in the specification, to meet the written description requirement. *Falko-Gunter Falkner*, 448 F.3d at 1366; *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575-76 (Fed. Cir. 1985) (holding that specification’s disclosure preferring a lower operating range, yet indicating no upper limit, combined with the industry knowledge at the time, was sufficient for a POSA to discern that higher ranges could be used); *see also Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1154 (Fed. Cir. 2004). . “The written description requirement is met when the disclosure allows one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. There is no rigid requirement that the disclosure contain either examples or an actual reduction to practice”; the proper inquiry is whether the patentee has provided an adequate description that “in a definite way identifies the claimed invention in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing. That assessment “requires

an objective inquiry into the four corners of the specification, as the hallmark of written description is disclosure.” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015) (internal quotation marks and citations omitted).

248. A claim will not be invalidated simply because the embodiments of the specification do not contain examples or testing relating to every possible embodiment of the claims. *See Ralston Purina*, 772 F.2d at 1575–76 (holding that specification’s disclosure preferring a lower operating range, yet indicating no upper limit, combined with the industry knowledge at the time, was sufficient for a POSA to discern that higher ranges could be used); *see also Lampi Corp. v. Am. Power Prods., Inc.*, 228 F.3d 1365, 1378 (Fed. Cir. 2000) (holding written description sufficient to support claims covering non-identical half-shells where patent drawings, the only cited written description support, only disclosed identical half-shells).

249. In particular, “analogizing a subset of patients having a variant of a particular disease to traditional genus and species claims is inapt. It would be incorrect to fractionate a disease or condition that a method of treatment claim is directed to, and to require a separate disclosure in the specification for each individual variant of the condition . . . in order to satisfy the enablement and written description provisions of 35 U.S.C. § 112, unless these variants are specified in the claims.” *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1371 (Fed. Cir. 2023). “[F]or any given method of treatment claim, there may be a subset of patients who would not benefit from or should not take the claimed treatment. That does not mean that such claims are not sufficiently enabled or supported by written description. A subset of unresponsive patients is not analogous to unsupported species in a generic claim to chemical compounds.” *Id.* (citation omitted).

250. A specification implicitly satisfies the written description requirement if a POSA

would find it “reasonably clear what the invention is and that the patent specification conveys that meaning.” *All Dental Prodx.*, 309 F.3d at 779. That is, the “reasonably conveys” standard does not require the disclosure and claims to match exactly. *Ariad Pharms.*, 598 F.3d at 1352 (“[T]he [written] description requirement does not demand any particular form of disclosure or that the specification recite the claimed invention in haec verba.”).

251. Enablement “is limited to what is claimed. Section 112 requires enablement of ‘only the claimed invention,’ not matter outside the claims.” *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020); *In re Entresto*, 125 F.4th 1090, 1098 (Fed. Cir. 2025). “[T]he word ‘comprising’ in a claim ‘creates a presumption that the recited elements are only a part of the device, that the claim does not exclude additional, unrecited elements.’” *Tech. Consumer Prods., Inc. v. Lighting Sci. Grp. Corp.*, 955 F.3d 16, 22 (Fed. Cir. 2020) (quoting *Crystal Semiconductor Corp. v. TriTech Microelecs. Int’l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001)).

252. A failure to “specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented.” *All Dental Prodx.*, 309 F.3d at 779.

### **c) Enablement**

253. To enable a patent claim, the patent specification “shall contain . . . the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]” 35 U.S.C. § 112.

254. Enablement is a question of law based on underlying facts that is determined from the perspective of the person of ordinary skill and is made retrospectively by looking back to “the

filing date of the patent application.” *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

255. “Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation.” *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 981 (Fed. Cir. 2021) (internal quotation marks omitted); *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988); *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. 2003) (“The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without ‘undue experimentation.’” (citations omitted)).

256. “Factors for assessing whether a disclosure would require undue experimentation include: ‘(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.’” *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 981 (Fed. Cir. 2021) (quoting *In re Wands*, 858 F.2d at 737).

257. “[T]he enablement requirement is met if the description enables any mode of making and using the invention.” *Invitrogen*, 429 F.3d at 1070-71 (quoting *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998)). The Federal Circuit “has repeatedly made clear, the specification need not include a working example of every possible embodiment to enable the full scope of the claims.” *Bayer Healthcare*, 989 F.3d at 982. Moreover, as discussed above, the Federal Circuit has held that “[i]t would be incorrect to fractionate a disease or condition that a method of treatment claim is directed to, and to require a separate disclosure in the

specification for each individual variant of the condition . . . in order to satisfy the enablement and written description provisions of 35 U.S.C. § 112, unless these variants are specified in the claims.”

*United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1371 (Fed. Cir. 2023).

258. “An artisan’s knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art, and a patent need not teach, and preferably omits, what is well known in the art.” *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1102 (Fed. Cir. 2020) (internal quotation marks and citations omitted). Accordingly, “[t]he question of undue experimentation is a matter of degree, and what is required is that the amount of experimentation not be ‘unduly extensive.’” *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1338 (Fed. Cir. 2013) (quoting *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004). “In addition, extensive experimentation does not necessarily render the experiments unduly extensive where the experiments involve repetition of known or commonly used techniques.” *Id.*

259. “Even if some of the claimed combinations” in a patent’s scope are “inoperative, the claims are not necessarily invalid. ‘It is not a function of the claims to specifically exclude . . . possible inoperative substances.’” *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) (quoting *In re Dinh-Nguyen*, 492 F.2d 856, 858–59 (CCPA 1974)). Furthermore, as discussed above, “for any given method of treatment claim, there may be a subset of patients who would not benefit from or should not take the claimed treatment. That does not mean that such claims are not sufficiently enabled or supported by written description. A subset of unresponsive patients is not analogous to unsupported species in a generic claim to chemical compounds.” *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1371 (Fed. Cir.

2023) (citation omitted). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co.*, 750 F.2d at 1576-77 (Fed. Cir. 1984).

260. Given that experimentation is allowed and that it would be undesirable to require patents to disclose all details that are within the knowledge of the person of ordinary skill, the Federal Circuit has instructed that “it is unnecessary to spell out every detail of the invention in the specification” and the patent application does not need to disclose specific examples corresponding to every claimed embodiment. *See Falko-Gunter Falkner*, 448 F.3d at 1366 (citation omitted); *see also Koito Mfg. Co.*, 381 F.3d at 1156 (“This Court has repeatedly explained that a patent applicant does not need to include in the specification that which is already known to and available to one of ordinary skill in the art.”). As such, § 112 requires only a “reasonable correlation” between the disclosure and the claims. *Invitrogen*, 429 F.3d at 1071 (citation omitted).

261. “[O]ne [can]not use a later-existing state of the art to invalidate a patent that was enabled for what it claimed at the time of filing.” *In re Entresto*, 125 F.4th 1090, 1099 (Fed. Cir. 2025) (quoting *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1340 (Fed. Cir. 2003)).

## **7. Inventorship**

262. The inventors named on an issued patent are presumed to be correct. *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1358 (Fed. Cir. 2004); *Nartron Corp. v. Schukra U.S.A. Inc.*, 558 F.3d 1352, 1356 (Fed. Cir. 2009); *see also Allergan, Inc. v. Teva Pharms. USA, Inc.*, No. 2:15-CV-1455-WCB, 2017 WL 4803941, at \*56 (E.D. Tex. Oct. 16, 2017) (Bryson, J.) (“In a case in which it is difficult to pinpoint a single individual or set of individuals who conceived of the

invention and then reduced it to practice, it is appropriate to invoke the presumption of correct inventorship, thus respecting the decision of the collaborators on the research project to resolve among themselves the credit for an invention that may have been more collectively stumbled upon than individually devised.”), *aff’d*, 742 F. App’x 511 (Fed. Cir. 2018). Thus, a party alleging non-joinder of an inventor must meet the heavy burden of proving her case by clear and convincing evidence. *Eli Lilly v. Aradigm*, 376 F.3d at 1358. The clear and convincing burden of proof is applied to joint inventorship disputes because of a “strong temptation for persons who consulted with the inventor and provided him with materials and advice, to reconstruct, so as to further their own position, the extent of their contribution to the conception of the invention.” *Eli Lilly v. Aradigm*, 376 F.3d at 1367; *see also Hess v. Advanced Cardiovascular Sys., Inc.*, 106 F.3d 976, 980 (Fed. Cir. 1997) (“[T]he temptation for even honest witnesses to reconstruct, in a manner favorable to their own position, what their state of mind may have been years earlier, is simply too great to permit a lower standard . . . . This language is similarly applicable to claims of co-inventorship made after a patent has been issued—particularly where, as here, the patent has been outstanding for a considerable time and the patented device has been successful. In that situation, too, there is an equally strong temptation for persons who consulted with the inventor and provided him with materials and advice, to reconstruct, so as to further their own position, the extent of their contribution to the conception of the invention.” (internal quotation marks and citation omitted)). The clear and convincing standard applies without regard to the circumstances of a particular case. *Hess*, 106 F.3d at 980.

263. The party alleging non-joinder must provide evidence to corroborate the alleged joint inventor’s conception. *Eli Lilly v. Aradigm*, 376 F.3d at 1358; *Shu-Hui Chen v. Bouchard*, 347 F.3d 1299, 1309 (Fed. Cir. 2003) (“It is well established that when a party seeks to prove



conception via the oral testimony of a putative inventor, the party must proffer evidence corroborating that testimony.”). Because conception is a mental act, courts require “corroborating evidence of a contemporaneous disclosure that would enable one skilled in the art to make the invention.” *Burroughs Wellcome Co. v. Barr Lab’ys, Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). “[I]f there is no evidence in record that all of the elements of the count resided in the inventor’s mind, a noninventor’s testimony cannot supply the missing pieces.” *In re Jolley*, 308 F.3d 1317, 1325 (Fed. Cir. 2002). The sufficiency of corroborating evidence is evaluated under a “rule of reason analysis, which requires that an evaluation of all pertinent evidence must be made so that a sound determination of the credibility of the inventor’s story may be reached.” *Plastipak Packaging, Inc. v. Premium Waters, Inc.*, 55 F.4th 1332, 1340 (Fed. Cir. 2022) (internal quotation marks omitted); *E.I. du Pont De Nemours & Co. v. Unifrax I LLC*, 921 F.3d 1060, 1076 (Fed. Cir. 2019).

264. A joint invention is the product of a collaboration between two or more people working together to solve a problem. *Burroughs*, 40 F.3d at 1227. Two people may be joint inventors even if they do not physically work on the invention together or at the same time, and even if they do not make the same type or amount of contribution. *Id.* However, there must be some element of joint behavior—that is, inventors must have “some open line of communication during or in temporal proximity to their inventive efforts.” *Eli Lilly v. Aradigm*, 376 F.3d at 1359.

265. To be a joint inventor, a person must contribute to the “conception of at least one claim of the patent that is not insignificant in quality, when that contribution is measured against the dimension of the full invention.” *CardiAQ Valve Techs., Inc. v. Neovasc Inc.*, 708 F. App’x 654, 658 (Fed. Cir. 2017) (internal quotation marks omitted); *Eli Lilly v. Aradigm*, 376 F.3d at 1358, 1361-62; *Nartron*, 558 F.3d at 1356-57. “Because co-inventors need not ‘make a

contribution to the subject matter of every claim of the patent,’ inventorship is determined on a claim-by-claim basis.” *Trovan, Ltd. v. Sokymat SA, Irori*, 299 F.3d 1292, 1302 (Fed. Cir. 2002) (citation omitted) (quoting *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998)). A contribution to realizing an invention does not amount to a contribution to conception if the alleged inventor merely explains well-known concepts or the “state of the art,” if the contribution is focused solely on the realization of the invention, or if the contribution is “too far removed from the real-world realization of an invention.” *Eli Lilly v. Aradigm*, 376 F.3d at 1359.

266. Conception is the “completion of the mental part of invention”—“the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.” *Burroughs*, 40 F.3d at 1228 (citation omitted); *see also Ethicon*, 135 F.3d at 1460. An idea is sufficiently definite and permanent when “the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue.” *Burroughs*, 40 F.3d at 1228-29 (“Nor do we suggest that a bare idea is all that conception requires”); *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 891 F. Supp. 2d 588, 646 (D. Del. 2012) (Stark, J.), *rev’d on other grounds*, 737 F.3d 731 (Fed. Cir. 2013) (Named inventor “supervised the implementation and completion of the Phase II study, as well as the analysis and interpretation of clinical data as reported in the patents, and also was involved throughout [patentee]’s regulatory submissions to the FDA. [Named inventor’s] role in conducting and interpreting the Phase II clinical trial results was critical to the inventors’ ability to meaningfully describe their invention. Otherwise, the patents-in-suit would have provided nothing more than ‘a mere wish or plan’ to obtain the claimed invention and, thus, would have failed to adequately describe the claimed invention.”); *Purdue Pharma L.P. v. Accord Healthcare Inc.*, 669 F. Supp. 3d 286, 312 (D. Del. 2023) (finding no conception where “memo to [alleged inventor’s]

supervisor said that ‘it was difficult to be certain’ that [feature of claimed compound] was responsible for the challenges [encountered] . . . and that it ‘warranted further investigation.’”); *Allergan*, No. 2:15-CV-1455-WCB, 2017 WL 4803941, at \*55 (“[T]he ‘invention’ in this case was the product of clinical testing results that the test designers, according to their testimony, did not expect. There was no conception of the invention prior to the analysis of the experimental results.”). Thus, conception is complete only “when the idea is so clearly defined in the inventor’s mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation.” *Burroughs*, 40 F.3d at 1228. In other words, the idea must “involve[] a specific approach to the particular problem” and must be “sufficiently precise that a skilled artisan could carry out the invention without undue experimentation.” *Id.* at 1229-30.

267. “[W]here the idea is in constant flux, it is not definite and permanent. A conception is not complete if the subsequent course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor’s idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice.” *Id.* at 1290. While “an inventor need not know that his invention will work for conception to be complete,” he must “possess an operative method of making the invention.” *Dawson v. Dawson*, 710 F.3d 1347, 1356 (Fed. Cir. 2013) (alterations and citation omitted). “These rules ensure that patent rights attach only when an idea is so far developed that the inventor can point to a definite, particular invention.” *Burroughs*, 40 F.3d at 1228.

268. In the context of joint inventorship, “[o]ne who merely suggests an idea of a result to be accomplished, rather than means of accomplishing it, is not a joint inventor.” *Nartron*, 558 F.3d at 1359 (citation omitted) (“An entrepreneur’s request to another to create a product that will fulfill a certain function is not conception—even if the entrepreneur supplies continuous input on

the acceptability of offered products.” (citation omitted)); *Morgan v. Hirsch*, 728 F.2d 1449, 1452 (Fed. Cir. 1984) (“[A]sking someone to produce something without saying just what it is to be or how to do it is not what the patent law recognizes as inventing . . . . Mr. Morgan has confused his entrepreneurship with inventorship.”). “[I]nventors may consult with others in the course of development without rendering each consultant a co-inventor.” *Abbott Biotechnology Ltd. v. Centocor Ortho Biotech, Inc.*, 35 F. Supp. 3d 163, 171 (D. Mass. 2014); *see also Huck Mfg. Co. v. Textron, Inc.*, No. 35956, 1975 WL 21108, at \*27 (E.D. Mich. May 2, 1975) (“The suggestion or conception of an idea or appreciation of a result to be accomplished, rather than the means of accomplishing it, particularly when the means constitute an essential part of the invention, does not constitute joint or sole inventorship. The mere fact that others made suggestions and possibly gave assistance does not necessarily make them inventors.”).

269. A joint inventor must make a contribution to the claimed invention “that is not insignificant in quality, when that contribution is measured against the dimension of the full invention.” *CardiAQ*, 708 F. App’x at 658 (citation omitted). Even if “a component [is] essential to an invention, [it] is an insufficiently significant contribution if the component and the principles of its use were known in the prior art.” *Bard Peripheral Vascular, Inc. v. W.L. Gore & Assocs., Inc.*, 776 F.3d 837, 845 (Fed. Cir. 2015), *abrogated on other grounds by Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 579 U.S. 93 (2016); *compare Maatuk v. Emerson Elec., Inc.*, 781 F. App’x 1002, 1006 (Fed. Cir. 2019) (finding contribution of two claim limitations insignificant because they were disclosed in the prior art), *with In re VerHoef*, 888 F.3d 1362, 1366 (Fed. Cir. 2018), *as amended* (May 7, 2018) (finding component essential because it distinguished the claimed invention over the prior art).

270. “One who simply provides the inventor with well-known principles or explains the

state of the art without ever having a ‘firm and definite idea’ of the claimed combination as a whole does not qualify as a joint inventor.” *Ethicon*, 135 F.3d at 1460 (citation omitted); *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997). An alleged co-inventor does not contribute to conception when he merely discloses an available product, discusses its properties, and explains how it could and might be used in an invention. *Hess*, 106 F.3d at 979-80. In doing so, an alleged co-inventor does “no more than a skilled salesman would do in explaining how his employer’s product could be used to meet a customer’s requirements.” *Id.* at 981.

271. Even if the party challenging inventorship is ultimately successful in proving an incorrect inventorship, a patentee may still correct that error in inventorship either upon petition to the Director or upon court order pursuant to 35 U.S.C. § 256. “Whenever through error a person is named in an issued patent as the inventor, or through error an inventor is not named in an issued patent, the Director may, on application of all the parties and assignees, with proof of the facts and such other requirements as may be imposed, issue a certificate correcting such error.” 35 U.S.C. § 256(a).

272. The Federal Circuit has held that § 256 recognizes that the “error of omitting inventors or naming persons who are not inventors *shall not invalidate the patent* in which such error occurred if it can be corrected as provided in this section.” *Egenera, Inc. v. Cisco Sys., Inc.*, 972 F.3d 1367, 1376 (Fed. Cir. 2020) (emphasis in original) (quoting 35 U.S.C. § 256(b)). Further, that “error” in § 256 includes “all varieties of mistakes – honest and dishonest” rather than only unintentional accuracy. *Id.* Even if the error was made with deceptive intention, correction is the appropriate remedy, not invalidation. *Id.* at 1377 (The AIA amended § 256(b) to specify that error “does not exclude ‘considered acts,’ or even ‘deceptive intention’ . . . ‘Error’ is simply the incorrect listing of inventors.”). Section 256 is a “savings provision” with no limitations period –

inventorship can be corrected at any time. *Magnetar Techs. Corp. v. Six Flags Theme Parks Inc.*, 2017 WL 3279120, at \*4 (D. Del. 2017) (“If a patentee demonstrates that inventorship can be corrected as provided for in section 256, a district court must order correction of the patent, thus saving it from being rendered invalid.” (alteration and citation omitted)).

273. The correction of inventorship via a certificate of correction under 35 U.S.C. § 256 applies retroactively, regardless of whether the certificate was filed after the commencement of an action. *See Roche Palo Alto LLC v. Ranbaxy Lab ’ys Ltd.*, 551 F. Supp. 2d 349, 350-51 (D.N.J. 2008) (making clear that correction under § 256 applies retroactively, unlike corrections under other sections). Corrections of inventorship pursuant to § 256 are not viewed as a substantive change in the scope of the patent. *Id.* at 358. Further, the Federal Circuit has made clear that correction of “error[s]” under “§ 256 does not exclude ‘considered acts,’ or even ‘deceptive intention,’ from the meaning of ‘error.’” *Egenera, Inc. v. Cisco Sys., Inc.*, 972 F.3d 1367, 1377 (Fed. Cir. 2020). The Federal Circuit has applied this principle to remove prior art after the correction of inventorship. *Riverwood Int’l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1357 (Fed. Cir. 2003); *see also Roche*, 551 F. Supp. 2d at 357-59 (analyzing case law and statutory basis for retroactive applicability of certificate of correction under § 256).

## **B. Contested Issues of Law**

### **1. POSA, Priority Date, and Prior Art**

274. Defining a person of ordinary skill in the art with respect to claims 1-11 and 14-19 of the ’327 patent.

275. Whether UTC has met its burden of production to show that at least claims 1-2, 6-11, and 14-16 of the ’327 patent are entitled to claim priority to the ’810 Provisional.

276. Whether—after UTC has met its burden of production to show that at least claims

1-2, 6-11, and 14-16 of the '327 patent are entitled to claim priority to U.S. Provisional Application No. 63/011,810, filed on April 17, 2020—Defendant has proven, by clear and convincing evidence, that at least claims 1-2, 6-11, and 14-16 of the '327 patent are not entitled to claim priority to the '810 Provisional.

277. Whether Plaintiff has met its burden of production to show that the 2020 Press Release meets the requirements of the prior art exception set forth in 35 U.S.C. § 102(b)(1)(A).

278. Whether Defendant has proven, by clear and convincing evidence, that the February 2020 Press Release is prior art to each asserted claim of the '327 patent under 35 U.S.C. § 102(a)(1).

279. Whether Plaintiff has met its burden of production to show that the '793 patent meets the requirements of the prior art exception set forth in 35 U.S.C. § 102(b)(2)(C).

280. Whether Defendant has proven, by clear and convincing evidence, that the '793 patent is prior art to each asserted claim of the '327 patent under 35 U.S.C. § 102(a)(1) and/or 35 U.S.C. § 102(a)(2).

281. Whether Defendant has proven, by clear and convincing evidence, that Saggart 2014, Agarwal 2015, Parikh 2016, 2009 Tyvaso® Label, and 2017 INCREASE Study Description prior art to each asserted claim of the '327 patent under 35 U.S.C. § 102(a)(1).

## **2. Validity of the '327 Patent**

### **a) Anticipation**

282. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 15-19 of the '327 patent are invalid as anticipated under 35 U.S.C. § 102.

283. Whether Defendant has proven, by clear and convincing evidence, that claims 1-4, 6-8, 11, and 15-19 of the '327 patent are anticipated by the February 2020 Press Release.

284. Whether Defendant has proven, by clear and convincing evidence, that claims 1-3,

6-8, 11, and 15-19 of the '327 patent are anticipated by Faria-Urbina 2018.

285. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 15-19 of the '327 patent are invalid as inherently anticipated under 35 U.S.C. § 102.

286. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 15-19 of the '327 patent are inherently anticipated by Faria-Urbina 2018.

287. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 15-19 of the '327 patent are inherently anticipated by the 2017 INCREASE Study Description.

288. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 15-19 of the '327 patent are inherently anticipated by the 2009 Tyvaso Label.

289. Whether Defendant has proven, by clear and convincing evidence, that claims 1-3, 6, 11, and 15-19 of the '327 patent are inherently anticipated by Agarwal 2015.

290. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 14-19 of the '327 patent are invalid under 35 U.S.C. § 102 for being on sale prior to the effective filing date of the '327 patent.

291. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 14-19 of the '327 patent are invalid under 35 U.S.C. § 102 for being in public use prior to the effective filing date of the '327 patent.

**b) Obviousness**

292. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 14-19 of the '327 patent are invalid as obvious pursuant to 35 U.S.C. § 103.

293. Whether Defendant has proven, by clear and convincing evidence, that claims 9-10 and 14 of the '327 patent are obvious over the February 2020 Press Release in combination with the '793 patent and/or Saggar 2014.

294. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11



and 14-19 of the '327 patent are obvious over Faria-Urbina 2018 in combination with the '793 patent and/or Saggar 2014.

295. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 14-19 of the '327 patent are obvious over Agarwal 2015 in combination with the '793 patent and/or Saggar 2014.

296. Whether objective indicia of nonobviousness rebut any *prima facie* evidence of obviousness Defendant has offered regarding claims 1-11 and 14-19 of the '327 patent.

297. Whether the inventions claimed in the '327 patent demonstrated unexpected results.

298. Whether there was skepticism by those in the art regarding inventions claimed in the '327 patent.

299. Whether others in the field had tried and failed to accomplish the inventions claimed in the '327 patent.

300. Whether the inventions claimed in the '327 patent satisfied a long-felt but unmet need in the art.

301. Whether the prior art taught away from the inventions claimed in the '327 patent.

302. Whether the inventions claimed in the '327 patent were the subject of industry praise.

303. Whether the inventions claimed in the '327 patent were commercially successful.

304. Whether others—including Defendant—have copied the inventions claimed in the '327 patent.

305. Whether a sufficient nexus exists between the inventions claimed in the '327 patent and any alleged objective indicia of nonobviousness.

**c) Written Description**

306. Whether Defendant has proven, by clear and convincing evidence, that claims 9-10

of the '327 patent are invalid under 35 U.S.C. § 112(a) for lack of written description.

**d) Inventorship**

307. Whether Defendant has proven, by clear and convincing evidence, that claims 1-11 and 14-19 of '327 patent is invalid for incorrect inventorship.

**3. Remedy**

308. Whether UTC is entitled to judgment that claims 1-11 and 14-19 of the '327 patent are not invalid.

**V. ENFORCEABILITY**

**A. Inequitable Conduct**

309. “To prevail on the defense of inequitable conduct, the accused infringer must prove that the applicant misrepresented or omitted material information with the specific intent to deceive the PTO .... by clear and convincing evidence.” *Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276, 1287 (Fed. Cir. 2011); *see also Network Signatures, Inc. v. State Farm Mut. Auto. Ins. Co.*, 731 F.3d 1239, 1242, 1243 n.2 (Fed. Cir. 2013) (noting that “[t]he facts of materiality and intent must be established by clear and convincing evidence” and rejecting argument that the preponderance of the evidence standard applies to materiality). Clear and convincing evidence must “place[ ] in the fact finder ‘an abiding conviction that the truth of the factual contentions are highly probable[,]’” *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009), and should “instantly tilt[ ] the evidentiary scales” in favor of its proponent when weighed against the opposing evidence. *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984). The Federal Circuit articulated this strict standard, in part, to stem the “plague” of inequitable conduct allegations asserted on the “slenderest of grounds.” *Therasense*, 649 F.3d at 1289 (citations omitted).

310. A reference must be “withheld” before there can be any finding of inequitable conduct. *See id.* at 1291–92. “When a reference was before the examiner, whether through the examiner’s search or the applicant’s disclosure, it cannot be deemed to have been withheld from the examiner.” *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1582 (Fed. Cir. 1991) (overruled on other grounds); *Sash Controls, Inc. v. Talon, L.L.C.*, 185 F.3d 882, at \*5 (Fed. Cir. 1999); *Fiskars, Inc. v. Hunt Mfg. Co.*, 221 F.3d 1318, 1327 (Fed. Cir. 2000) (“[A]n applicant can not be guilty of inequitable conduct if the reference was cited to the examiner[.]”); *Rogers P. Jackson v. Nuvasive*, No. 21-53, 2023 WL 6387866, at \*3 (D. Del. Sept. 29, 2023); *Symbol Techs., Inc. v. Aruba Networks, Inc.*, 609 F. Supp. 2d 353,358 (D. Del. 2009).

311. Only if a court determines that a reference was not before the PTO during a patent’s prosecution will the court consider whether an accused infringer has proven two distinct inequitable conduct elements: materiality and deceptive intent. *Therasense*, 649 F.3d at 1290. In assessing these requirements, “[a] district court should not use a ‘sliding scale,’ where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa. Moreover, a district court may not infer intent solely from materiality.” *Id.* “And even if this elevated evidentiary burden is met as to both elements, the district court must still balance the equities to determine whether the applicant’s conduct before the PTO was egregious enough to warrant holding the entire patent unenforceable. Thus, even if a threshold level of both materiality and intent to deceive are proven...the court may still decline to render the patent unenforceable.” *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008).

312. The “materiality” required to establish inequitable conduct is “but-for materiality.” *Id.* at 1291. A reference is but-for material if the PTO would not have allowed a claim had it been aware of the reference. *Id.* “[T]he Federal Circuit has held that failure to disclose litigation, without

more, is not sufficient to establish materiality.” *CFL Techs. LLC v. Osram Sylvania, Inc.*, No. 1:18-CV-01445-RGA, 2019 WL 2995815 at \*6 (D. Del. July 9, 2019) (finding no inequitable conduct where applicant did not disclose ongoing litigation “directed to the same general subject matter as the pending applications”).

313. “Prior art is not but-for material if it is merely cumulative.” *California Inst. of Tech. v. Broadcom Ltd.*, 25 F.4th 976, 991 (Fed. Cir. 2022); *see also Dig. Control Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1319 (Fed. Cir. 2006); *Rolls-Royce Ltd. v. GTE Valeron Corp.*, 800 F.2d 1101, 1107 (Fed. Cir. 1986) (“Nothing in law or logic . . . requires an applicant to submit non-material, merely cumulative references for PTO review.”). The burden of demonstrating non-cumulativeness lies with the accused infringer; the patent owner does not have the burden to demonstrate cumulativeness. *Intermec Techs. Corp. v. Palm Inc.*, 738 F. Supp. 2d 522, 561 (D. Del. 2010) (rejecting accused infringer’s argument that he did not need to demonstrate non-cumulativeness because patentee had not shown that any references were cumulative, noting that “[t]he burden to show that non-disclosed prior art was cumulative . . . cannot be shifted to [patent owner].”) “The need to strictly enforce the burden of proof . . . in the inequitable conduct context is paramount because the penalty for inequitable conduct is so severe.” *Star*, 537 F.3d at 1365.

314. Cumulativeness must be assessed with respect to “particular claim limitations” that are supposedly absent from the prior art before the examiner. *St. Jude Med., Cardiology Div., Inc. v. Volcano Corp.*, 2014 WL 2622240, at \*1 (D. Del. June 11, 2014); *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1329-30 (Fed. Cir. 2009) (defendant must identify specific claim limitations allegedly absent in prior art of record). Whether the examiner understood the prior art before him is irrelevant to determining whether an undisclosed reference is cumulative, because the examiner is presumed to have read and understood the art cited during the prosecution of a

patent. *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984) (“[E]xaminers . . . are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art.”), *abrogated on other grounds by Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276 (Fed. Cir. 2011); *see also Astrazeneca Pharms. LP v. Mayne Pharma (USA) Inc.*, 2005 WL 2864666, at \*26 (S.D.N.Y. Nov. 2, 2005) (“‘An applicant cannot be guilty of inequitable conduct if the reference was cited to the examiner, whether or not it was a ground of rejection by the examiner.’ ‘The Patent Examiner is presumed to have read and understood the art cited during the prosecution of a patent.’”) (citations omitted); *Prima Tek II, L.L.C. v. Polypap Sarl*, 316 F. Supp. 2d 693, 710 (S.D. Ill. 2004) (rejecting argument that applicant misled the examiner during prosecution by failing to point out a particular statement in a prior art reference that purportedly would have rendered claim unpatentable, because “[t]he PTO examiner is presumed to have read the [reference] in its entirety.”).

315. With respect to the “specific intent” element, the accused infringer must provide clear and convincing evidence of “deceptive intent,” which requires it to “prove that the patentee acted with the specific intent to deceive the PTO.” *Therasense*, 649 F.3d at 1290. “[T]he evidence must be ‘sufficient to *require* a finding of deceitful intent in the light of all the circumstances’; deceptive intent ‘must be the single most reasonable inference able to be drawn from the evidence’; and ‘when there are multiple reasonable inferences that may be drawn, intent to deceive cannot be found.’” *Intercontinental Great Brands LLC v. Kellogg N. America Co.*, 869 F.3d 1336, 1351 (Fed. Cir. 2017) (quoting *Therasense*, 649 F.3d at 1290–91). Specifically, “the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it.” *Therasense*, 649 F.3d at 1290. An inference of deceptive intent cannot rely on knowledge alone. *Exergen Corp. v. Wal-Mart Stores*,

*Inc.*, 575 F.3d 1312, 1328 (Fed. Cir. 2009). Nor will an inference of deceptive intent follow from the fact that a withheld reference is ultimately found to be material, or because a party “should have known” about the materiality of a reference. *Therasense*, 649 F.3d at 1290 (explaining that “[i]ntent and materiality are separate requirements,” and that “[p]roving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive.”). Rather, “there must be a *factual* basis for a finding of deceptive intent.” *Optium Corp. v. Emcore Corp.*, 603 F.3d 1313, 1321 (Fed. Cir. 2010).

316. Where an applicant disclosed the existence of proceedings, but failed to provide particular filings from those proceedings, “the more likely inference that can be drawn is that prosecution counsel believed he had satisfied his duty of candor when he informed the Examiner of the [proceedings].” *Tinnus Enter., LLC v. Telebrands Corp.*, No. 6:16-CV-00033-RWS, 2017 WL 8727626, at \*3-4 (E.D. Tex. Aug. 15, 2017) (finding no inequitable conduct where patent owner identified PGR proceeding but failed to disclose institution decision because the PTO can readily obtain “documents from its own administrative agency when necessary.”); *DynaEnergetics Eur. GmbH v. Hunting Titan, Inc.*, 629 F. Supp. 3d 548, 574 (S.D. Tex. 2022) (finding no inequitable conduct where patent owner identified IPR proceeding but failed to disclose final written decision because (1) the IPR petition was disclosed to the Examiner, (2) “the IPR FWD is a publicly available document,” (3) “the PTAB is an administrative agency of the USPTO” that could have obtained the FWD, and (4) “the IPR FWD is neither prior art, nor binding precedent.”); *Affinity Labs of Texas, LLC v. Netflix, Inc.*, No. 1:15-CV-849-RP, 2016 WL 11782866, at \*4 (W.D. Tex. Aug. 22, 2016) (finding no inequitable conduct where applicant disclosed IPR petition and supporting declarations for related patent, but failed to disclose institution decision because, in part, the examiner had “access to the parties’ arguments on the petition.”).

317. “Because the party alleging inequitable conduct bears the burden of proof, the ‘patentee need not offer any good faith explanation unless the accused infringer first . . . prove[s] a threshold level of intent to deceive by clear and convincing evidence.’” *Therasense*, 649 F.3d at 1291 (quoting *Star*, 537 F.3d at 1368 (alteration in original)).

## **B. Contested Issues of Law**

### **1. Inequitable Conduct**

318. Whether Defendant has proven, by clear and convincing evidence, that Mr. Stephen Maebius, Esq., committed inequitable conduct during the prosecution of the ’061 application.

319. Whether Defendant has proven, by clear and convincing evidence, that Mr. Shaun Snader, Esq., committed inequitable conduct during the prosecution of the ’061 application.

320. Whether Defendant has proven, by clear and convincing evidence, that Messrs. Snader and/or Maebius failed to disclose material information to the Patent Office during the prosecution of the ’061 application.

321. Whether Defendant has proven, by clear and convincing evidence, that the information it alleges Messrs. Snader and/or Maebius withheld from the Patent Office during prosecution of the ’061 application was not cumulative of the information that was already before the examiner.

322. Whether Defendant has proven, by clear and convincing evidence, that Messrs. Snader and/or Maebius withheld material information from the Patent Office during the prosecution of the ’061 application with the specific intent to deceive the Patent Office.

### **2. Remedy**

323. Whether UTC is entitled to judgment that the ’327 patent is enforceable.

## VI. EXCEPTIONAL CASE

### A. Legal Standards

324. Under 35 U.S.C. § 285 “[t]he court in exceptional cases may award reasonable attorney fees to the prevailing party.” A party seeking attorneys’ fees under § 285 must prove the merits of their contentions by a preponderance of the evidence. *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 572 U.S. 545, 557 (2014).

325. A finding of exceptional circumstances under 35 U.S.C. § 285, warranting an award of reasonable attorney fees, includes litigation conduct that causes competitive harm to a prevailing party. Such misconduct includes an alleged infringer’s attempt to conceal or misconstrue facts in support of the alleged infringer’s defense. *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1552 n.1 (Fed. Cir. 1989) (affirming the district court’s finding that the case was exceptional where the defendant was “engag[ing] in various discovery . . . abuses”).

326. “While the individual acts of misconduct might not make Defendants’ conduct look exceptional, Defendants’ conduct over the course of the entire litigation [may] support the conclusion [of] an exceptional case.” *See Drop Stop LLC v. Jian Qing Zhu*, 757 F. App’x 994, 999 (Fed. Cir. 2019) (internal quotation marks and alterations omitted). “[A] district court may award fees in the rare case in which a party’s unreasonable conduct—while not necessarily independently sanctionable—is nonetheless so ‘exceptional’ as to justify an award of fees.” *Octane Fitness*, 572 U.S. at 555. “[A] case presenting either subjective bad faith or exceptionally meritless claims may sufficiently set itself apart from mine-run cases to warrant a fee award.” *Id.*

327. When deciding whether a case is exceptional, the court must evaluate whether it “stands out from others with respect to the substantive strength of a party’s litigating position (considering both the governing law and the facts of the case) or the unreasonable manner in which



the case was litigated.” *Id.* “District courts may determine whether a case is ‘exceptional’ in the case-by-case exercise of their discretion, considering the totality of the circumstances.” *Id.*

328. The Court must consider a willfulness finding in assessing whether a case is exceptional under § 285; in the event of a willfulness finding, the district court must explicitly explain why the case is not exceptional despite the willfulness finding. *Whitserve, LLC v. Computer Packages, Inc.*, 694 F.3d 10, 37-38 (Fed. Cir. 2012). A willfulness finding, standing alone, can justify an exceptional case determination and award of attorneys’ fees under § 285. *See Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1373-74 (Fed. Cir. 2006). However, a willfulness finding is not a prerequisite to finding that a case is exceptional. *SRI Int’l, Inc. v. Cisco Sys., Inc.*, 14 F.4th 1323, 1332 (Fed. Cir. 2021) (“[T]he district court reconsidered attorney fees in the absence of a willfulness finding, and again found this case to be exceptional, justifying a full award of attorney fees. . . . We see no abuse of discretion by the district court in this regard and affirm its award of attorney fees.”) (internal quotation marks omitted).

329. A paragraph IV filing requires “a certification, in the opinion of the applicant and to the best of his knowledge, [that] each patent . . . for which the applicant is seeking approval . . . is invalid or will not be infringed.” 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (emphasis added).

330. 505(b)(2) Applicants owe a duty of care under the Hatch-Waxman Act when challenging patent validity. Applicants fail to meet this duty when they file “baseless” certifications. *Yamanouchi*, 231 F.3d at 1347-48; *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 549 F.3d 1381, 1388 (Fed. Cir. 2008).

## **B. Contested Issues of Law**

331. Whether this case is an exceptional case within the meaning of 35 U.S.C. § 285.

332. Whether UTC is entitled to recover its attorneys’ fees and costs.

ET one calendar day before they will be used at trial. For example, a listing of all exhibits intended for use during direct examination of non-adverse witnesses on Monday, June 23, 2025, would be exchanged by e-mail before 6:30 p.m. ET on Sunday, June 22, 2025.

48. The party receiving identification of exhibits intended for use in direct examination of non-adverse witnesses shall inform the party identifying the exhibits of any objections by 8:30 p.m. ET on the day of receipt, and the parties shall meet and confer as soon as possible thereafter, but by no later than 9:30 p.m. ET on the day of receipt to resolve such objections. Any unresolved objections shall be brought to the Court's attention for resolution no later than the start of the trial day on which the exhibit is intended to be used.

49. Prior to the start of direct examination of a particular witness, the party conducting the direct examination will provide the other party with two copies of binders containing all exhibits and demonstrative exhibits that they intend to use with that witness on direct examination and will provide all required copies to the Court. The parties agree that this provision does not require advance disclosure of exhibits to be used to impeach or on cross-examination of any witness. However, prior to the start of the cross-examination of any witness, the parties agree to provide the other with two copies of witness binders that contain all of the exhibits reasonably anticipated to be used on cross-examination of that witness and will provide all required copies to the Court.

## **VIII. WITNESSES**

50. Plaintiff's list of witnesses it may call live at trial or by deposition, together with Defendant's objections, is attached as Exhibit 6, and Exhibit 15 provides additional information on Plaintiff's experts' specialties and qualifications.

51. For witnesses that may appear by deposition, Plaintiff's list of deposition

designations, Defendant's objections to such designations, Defendant's counter-designations, and Plaintiff's objections to such counter-designations, is attached as Exhibit 8.

52. Defendant's list of witnesses it may call live at trial or by deposition, together with Plaintiff's objections, is attached as Exhibit 7, and Exhibit 16 provides additional information on Defendant's experts' specialties and qualifications.

53. For witnesses that may appear by deposition, Defendant's list of deposition designations, Plaintiff's objections to such designations, Plaintiff's counter-designations, and Defendant's objections to such counter-designations, is attached as Exhibit 9.

54. The listing of a witness on a party's pre-trial witness list does not require that party to call that witness to testify and does not necessarily mean that the listing party has the power to compel the live testimony of that witness.

55. The parties are not permitted to recall fact witnesses to testify multiple times; an expert witness may testify separately if solely on each of infringement and invalidity.

56. Any witness not listed on Exhibits 6 and 7 will be precluded from testifying at trial absent good cause shown. The parties reserve the right, however, to call one or more additional witnesses whose testimony is necessary to establish authenticity or admissibility of any trial exhibit, if the authenticity or admissibility of the exhibit is challenged by an opposing party.

57. The parties agree that each party may introduce any of its own affirmatively designated or counter-designated deposition testimony for a witness in response to the other party's deposition designations for that same witness. The parties may not introduce deposition designations or counter-designations, or provide new objections to listed designations or counter-designations that are not included in this Order except for good cause shown or by agreement of the parties. The parties may, however, add deposition designations solely to the extent necessary

to establish authenticity or admissibility of any trial exhibit, if the authenticity or admissibility of the exhibit is challenged by an opposing party.

58. The parties' witness lists represent the parties' good faith understanding and expectation about which witnesses are expected to be called live in person, or by deposition, at trial. To the extent that a witness's circumstances change, or a witness otherwise becomes unavailable for trial, each party reserves the right to call that witness by deposition to the extent permitted under the Federal Rules of Civil Procedure and the Federal Rules of Evidence and subject to resolution of any objections by the other party.

59. Each party will, with its best good faith understanding, identify by e-mail to the opposing party the witnesses it intends to call, including rebuttal witnesses, the order in which witnesses will be called, and whether those witnesses will be called live or by deposition, by 6:30 p.m. ET two calendar days before such witnesses will be called to testify. The parties reserve the right to revise, in good faith, their witness identifications, including order, following the close of the other party's case-in-chief or rebuttal case.

60. The other party will identify any objections to such witnesses via e-mail by 6:30 p.m. ET the following day, and the parties will meet and confer to resolve any objections by 9:30 p.m. ET that same evening. If good faith efforts to resolve any objections fail, the party objecting may bring its objections to the Court's attention prior to the witness being called to the witness stand. If later events cause the need to remove a witness from a party's witness list, the parties agree to notify the other side as soon as possible.

61. During adjournments in the trial including breaks during the trial and overnight, the offering party may discuss with a witness his or her testimony on direct examination until the witness is passed for cross-examination and cross-examination has commenced, but is prohibited

from discussing with the witness his or her testimony during cross-examination. Once cross-examination of the witness is concluded and the witness is passed for re-direct examination, the offering party may discuss with the witness his or her testimony on re-direct examination.

62. Unless otherwise agreed to between the parties, the party offering deposition testimony (other than for the purpose of impeachment) shall identify the deposition testimony to be offered, i.e., transcript page and line numbers exchanged designations, by 6:30 p.m. ET at least two calendar days prior to the testimony being offered into the record. The party receiving the designations shall inform the opposing party of any objections and counter-designations by 6:30 p.m. ET one calendar day prior to the testimony being offered into the record, and by 8:30 p.m. ET that same day, the introducing party will identify any objections to the other party's counter-designated testimony. The parties shall meet and confer to resolve any objections to designated testimony by 9:30 p.m. ET that same day to permit sufficient time to prepare any necessary video/DVD of the testimony. Any objections that cannot be resolved may be raised with the Court at the Court's convenience before trial resumes on the day of the anticipated use.

63. If applicable, a party's designation of a page and line from a particular transcript shall be automatically deemed to include any errata indicated for that page and line in the attached errata sheets.

64. To the extent that deposition designations or counter-designations are admitted into evidence, they must either be played by video or read in open court. If a party opts to introduce deposition testimony, any counter-designation of that same witness's testimony must be admitted in the same medium, and the testimony designated by both sides will be played or read consecutively in the sequence in which the testimony was originally given at deposition. If an exhibit is referenced in a deposition designation, the exhibit is admitted into evidence if it is

included on any party's trial exhibit list and is not otherwise objected to, subject to Section VII. A party may not affirmatively use deposition designations for a party's own officers and employees unless such party first satisfies a (Fed. R. Evid. 804) hearsay exception; however, either party may admit deposition designations for the other party's corporate representative, regardless of whether such witness may testify live (Fed. R. Evid. 801(d)(2)). A party may counter designate on such testimony as necessary for purpose of completeness based on what the opposing party has designated.

65. To the extent deposition designations are read or played in open court, each side will be charged the time taken to read or play its designations (or counter-designations). Specifically, any affirmative designations offered by a party will count against that party's trial presentation time whereas any counter-designations by the other party will count against the party who made the counter-designations. The time charged for designations played by video will be measured by the proportion of the number of lines of testimony for its designations to the total number of lines of testimony read, with any lines designated by both parties split equally. All irrelevant and redundant material, including colloquy between counsel and objections, will be eliminated when the deposition is played or read at trial.

66. The above procedures regarding deposition designations do not apply to portions of deposition transcripts and/or video of a witness used for impeachment or cross-examination of that witness. Any deposition testimony of a witness may be used at trial for the purpose of impeachment of that witness, regardless of whether a party specifically identified that testimony on its list of deposition designations, if the testimony is otherwise competent for such purpose.

#### **IX. STATEMENT OF ADDITIONAL MATTERS**

67. Plaintiff's statement of additional matters is attached as Exhibit 13.

68. Defendant's response to Plaintiff's statement of additional matters is attached as Exhibit 14

#### **X. BRIEF STATEMENT OF INTENDED PROOFS**

69. In support of its claims and defenses relating to the infringement and validity of the Patent-in-Suit, and in addition to the facts not in dispute, Plaintiff expects to offer the proofs attached as Exhibit 17.

70. In support of its claims and defenses relating to the noninfringement and invalidity of the Patent-in-Suit, and in addition to the facts not in dispute, Defendant expects to offer the proofs attached as Exhibit 18.

#### **XI. DESIRED AMENDMENTS TO THE PLEADINGS**

71. The time to amend the pleadings has passed. Plaintiff reserves the right to request amendment to the pleadings, and Defendants reserve the right to object.

#### **XII. CERTIFICATION OF SETTLEMENT DISCUSSIONS**

72. The parties have engaged in good faith efforts to explore resolution of this case by settlement. To date, no agreement has been reached between the parties.

#### **XIII. MOTIONS *IN LIMINE***

73. Pursuant to the Scheduling Order, any motions *in limine* filed by the parties, including motions, oppositions, and replies, shall be separately filed no later than the date on which the Pretrial Order is due. D.I. 45, ¶ 13.

#### **XIV. MISCELLANEOUS ISSUES**

##### **A. Damages**

##### **[[Plaintiff's Position:]]**

74. Plaintiff does not seek damages at this time and is not yet in a position to determine

if it may later seek damages, as there has been no commercial launch of Defendant's Proposed Product and Defendant has not produced sufficient material for Plaintiff to assess damages in the event of such launch. *See* Exhibit 13 at 2-4. Plaintiff reserves the right to seek attorneys' fees, costs, and expenses pursuant to 35 U.S.C. § 285. Plaintiff also reserves the right to seek damages if Defendant engages in the commercial manufacture, use, sale, offer to sell, and/or importation into the United States of the product that is the subject of Liquidia's 505(b)(2) Application before the expiration of the Patent-in-Suit, including any extension(s) and additional period(s) of exclusivity to which Plaintiff is or may become entitled. Plaintiff also reserves the right to seek damages for any infringing conduct by or attributable to Defendant that falls outside of the 35 U.S.C. § 271(e)(1) safe harbor.

**[[Defendant's Position:]]**

75. Throughout fact discovery, Plaintiff asserted to the Court that they are entitled to discovery directed to damages, including a reasonable royalty, and entitled to file expert reports on the issues of damages. *See* Exhibit 14, 3-4. Pursuant to an order from Judge Fallon, Defendants' produced information regarding sales projections and market forecasts for Yutrepia and offered on November 15, 2024 the Rule 30(b)(6) deposition of Defendant's CFO and COO, Michael Kaseta to occur on November 22, 2024. Plaintiff informed Liquidia on November 20, 2024 that UTC would not move forward with Mr. Kaseta's deposition until after November 26, 2024. Since then, UTC did not seek further recourse from the Court to substantiate any alleged failure by Defendant to produce documents pursuant to Judge Fallon's November 12, 2024 Order or that Plaintiff's production was deficient. As such, Plaintiff has waived its right to seek further discovery. Moreover, Plaintiff chose not to serve an expert report on the issue of damages and thus cannot seek damages in this pending Hatch-Waxman case. *See* Exhibit 14 at 3-4. Defendant



reserves the right to seek attorneys' fees, costs, and expenses pursuant to 35 U.S.C. § 285.

**B. Trial Parameters**

76. The bench trial in this case is currently scheduled to begin on June 23, 2025, with trial days from 8:30 a.m. ET to 5:00 p.m. ET, and is currently scheduled for three days, subject to the Court's availability. D.I. 45 at 9. UTC recommends truncating the trial to two days (with any permitted closing to occur on the third day), with each side allotted 7 hours. *See* Exhibit 13, at 5. UTC believes that two days is sufficient, particularly in view of the Court's May 21, 2025 Oral Order requiring UTC to reduce its asserted claims to no more than six, and for Liquidia to reduce its asserted invalidity / unenforceability defenses / counterclaims to no more than four. *See* D.I. 317. Indeed, during the parties' meet and confer on the pretrial order, Defendant stated it would consider agreeing to a two-day trial if UTC narrowed its asserted claims. Nevertheless, shortly before UTC's disclosure of only six asserted claims, Defendant again stated it would not agree to a two-day trial. Defendant does not agree with this recommendation given the number of claims the Plaintiff has asserted, the number of witnesses, and the number of issues in this case. *See* Exhibit 14, at 4-5. Defendant believes, despite the Court's May 21, 2025 Oral Order requiring the parties to reduce their asserted claims and defenses, that two days of trial time is still not sufficient because UTC still has multiple experts, including 2 on infringement, and a total of 30 witnesses. Furthermore, by maintaining claim 14 of the '327 patent, UTC asserts 7 claims, not 6, as the limitations of claim 11 will additionally need to be met for infringement. Defendant maintains that the disparate subject matter of the claims still asserted does not narrow the issues for trial and still necessitates three days of trial time.

77. Plaintiff and Defendant have each been allotted 10.5 hours to present their respective cases, which includes presenting opening statements, objecting to evidence in open

court, examining or cross-examining witnesses, presenting evidence by reading or playing a deposition transcript, or otherwise speaking or arguing on behalf of a party will be counted as the time of that party.

78. This is a non-jury trial.

79. The following order of proof currently applies at trial:

- a. Opening statements, in the following order: Plaintiff then Defendant;
- b. Plaintiff will present its case-in-chief on infringement;
- c. Defendant will present its rebuttal to infringement and its case-in-chief on invalidity;
- d. Plaintiff will present its rebuttal to invalidity; and
- e. Closing arguments, if the Court is inclined to hear them, will be delivered in the following order: Plaintiff, then Defendant. Any time used by a party for closing argument, if any, will not count against that party's 10.5 hours of trial time.

80. The Court has entered a Stipulated Protective Order to safeguard the confidentiality of certain of the parties' business and technical information, as well as that of third parties. *See* D.I. 48. All outside counsel shall handle such protected information in accordance with the terms of the Protective Order and shall not disclose such Protected Information to persons not authorized to view such information under the terms of the Stipulated Protective Order. Nonetheless, the presentation of evidence at trial shall take place in open court, unless a party specifically requests, and the Court agrees, that the Court be closed to the public during presentation of certain portions of the evidence.

### **C. Post-Trial Briefing**

81. The parties will coordinate with the Court at the conclusion of trial to provide a

post-trial briefing schedule. Prior to closing arguments, the parties will confer in attempt to reach a joint proposal for a post-trial briefing schedule.

**D. Order to Control Course of Action**

82. This order shall control the subsequent course of the action, unless modified by the Court to prevent manifest injustice or for good cause shown.

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May 23, 2025

**SO ORDERED** on this \_\_\_\_ day of \_\_\_\_\_, 2025.

\_\_\_\_\_  
United States District Judge